VOLUME 25 NUMBER 2

# ARCHIVES

OF

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FEBRUARY 16, 1920

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

# CONTENTS OF PREVIOUS NUMBERS

## OCTOBER, 1919. NUMBER 4


The Production of Bright's Disease by Feeding High Protein Diets. L. H. Newburgh, M.D., Ann Arbor, Mich.

Cutaneous Reaction and Desensitization in Quinin Idiosyncrasy. John J. O'Malley, M.D., and DeWayne G. Rickey, M.D., Washington, D. C.

Protozoologic and Clinical Studies on the Treatment of Protozoal Dysentery with Benzyl Benzoate. I. A Preliminary Report on Eight Cases of Endamebic Dysentery Treated at the Philippine General Hospital. Frank G. Haughwout, M.D., and Pedro T. Lantin, M.D., Manila, P. I., with an Addendum by M. A. Asuzano, M.D., Baguio, P. I.

A Statistical Discussion of the Relative Efficiency of Different Methods of Treating Pneumonia. Raymond Pearl, Baltimore.

The Basal Metabolism in Hypothyroidism. J. H. Means, M.D., and J. C. Aub, M.D., Boston.

The Relation of Neurocirculatory Asthenia to Hyperthyroidism as Determined by the Effects of the Injection of Epinephrin. Ernest P. Boas, M.D., New York.

The Significance of Abnormalities in the Form of the Electrocardiogram. G. Canby Robinson, M.D., St. Louis.

The Use of Laboratory Methods in the Diagnosis of Early Hyperthyroidism. Charles W. Lueders, M.D., Philadelphia.

The Control of Acidosis in the Treatment of Diabetes. Edgar Stillman, M.D., New York.

Sino-Atrial Heart Block in a Child. With Observations on the Effects of Atropin and Vagus Stimulation. N. Worth Brown, M.D., Baltimore.


## NOVEMBER, 1919. NUMBER 5


Factors Determining the Relative Intensity of the Heart Sounds in Different Areas. An Experimental Study. Carl J. Wiggers, M.D., Cleveland.

Prolongation of the "S-T" Interval of the Ventricular Complex as Shown by the Electrocardiograph. Jonathan Meakins, M.D., Montreal, Can.

Progressive Lenticular Degeneration Associated with Cirrhosis of the Liver (Wilson's Disease). C. P. Howard, M.D., and C. E. Royce, M.D., Iowa City, Iowa.

The Energy Index (S.D.R. Index) of the Circulatory System. Joseph H. Barach, M.D., Pittsburgh.

Meningococcus Meningitis at Camp Lee. Russell L. Haden, M.D. (Detroit), Camp Lee, Va.

The Cholesterol Content of the Blood in Various Hepatic Conditions. M. A. Rothschild, M.D., and J. Felsen, M.D., New York.

Three Cases of "Renal Glycosuria." Frederick M. Allen, M.D., Mary E. Wishart and L. Millard Smith, Lakewood, N. J.

A Group of Sixty-Eight Cases of Type I Pneumonia Occurring in Thirty Days at Camp Upton. With Special Reference to Serum Treatment. Charles F. Tenney, M.D. (Toledo), and William T. Rivenburgh, M.D. (Highland, N. Y.), Camp Upton, N. Y.

The Determination of Hemoglobin by the Acid Hematin Method. Louis Berman, New York.

A Study of the Renal Concentration Power for the Uric Acid in Early Chronic Interstitial Nephritis. Preliminary Paper. Roy Upham, M.D., and Henry Allen Higley, M.D., Brooklyn.

Roentgenographic Studies in Gout. C. W. McClure, M.D., and E. D. McCarty, M.D., Boston.


## DECEMBER, 1919. NUMBER 6


Botulism. A Study of the Resistance of the Spores of Bacillus Botulinus to Various Sterilizing Agencies Which Are Commonly Employed in the Canning of Fruits and Vegetables. Ernest C. Dickson, M.D., Georgina S. Burke, M.D., and Engelena S. Ward, A.M., San Francisco.

A Study of Pneumococcus Carriers. Joseph Sailer, M.D., Philadelphia; Milton W. Hall, M.D., Camp Jackson, S. C.; Robert L. Wilson, M.D., Jeannette, Pa., and Charles McCoy, M.D., M. C., U. S. Army.

The Basal Metabolism in Exophthalmic Goiter. J. H. Means, M.D., and J. C. Aub, M.D., Boston.

Antipyretics. I. The Benedict Respiration Chamber at the New Haven Hospital. Henry G. Barbour, M.D., New Haven, Conn.

Antipyretics. II. Acetylsalicylic Acid and Heat Regulation in Normal Individuals. Henry G. Barbour, M.D., and Michael M. Devenis, M.D., New Haven, Conn.

Antypyretics. III. Acetylsalicylic Acid and Heat Regulation in Fever Cases. Henry G. Barbour, M.D., New Haven, Conn.

Mental Disorders Following Influenza. Alfred Gordon, M.D., Philadelphia.

The Electrocardiogram and Ventricular Preponderance. Edward Perkins Carter, M.D., and Carl H. Greene, Ph.D., Baltimore.

The More Common Gases: Their Effect on the Respiratory Tract. Observation on Two Thousand Cases. Robert S. Berghoff, M.D., Chicago.

Index to Volume 24.


## JANUARY, 1920. NUMBER 1


Harmful Effects of Shallow Breathing with Special Reference to Pneumonia. Jonathan Meakins, M.D., Montreal.

Contributions to the Physiology of the Stomach. LII. Studies on Gastric Ulcer. A. C. Ivy, Ph.D., Chicago.

The Effect of Roentgen Rays on the Metabolism of Cancer Patients. Richard N. DeNiord, M.D.; Bernard F. Schreiner, M.D., and Hollis H. DeNiord, M.D., Buffalo.

The Cerebrospinal Fluid in Multiple Sclerosis. Joseph Earle Moore, M.D., Baltimore.

Cavity Formation and Annular Pleural Shadows in Pulmonary Tuberculosis. James A. Honeij, M.D., New Haven, Conn.

Rat Bite Fever. Report of a Case. Aaron Arkin, A.M., M.D., Ph.D., Morgantown, W. Va.

The Protein and Lipin Content of Blood Serum in the Nephritides. Max Kahn, M.D., Ph.D., New York.



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Archives of Internal Medicine

VOL. 25 FEBRUARY, 1920 No. 2

# A STUDY OF THE COLLOIDAL GOLD REACTION AND ITS CLINICAL INTERPRETATION *

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It was not until 1912 that Lange first presented the colloidal gold spinal fluid reaction which has since borne his name as well as the more common term, "gold-sol" reaction. In the comparatively short time which has elapsed since its advent, there has grown up on the subject a voluminous literature which has served to give the reaction a definite and well deserved place among the tests used as aids in the diagnosis of affections of the central nervous system. Further elucidation or discussion of the test may serve not so much for its justification as for a wider interpretation and broader understanding of this reaction and its relation to clinical symptoms. The best conditions for undertaking such a study will obtain, not in an insane hospital, dealing with mental cases alone, or even in a pure neurologic clinic, but in a general teaching hospital where all classes of cases are studied carefully from both laboratory and clinical points of view. In this manner an early diagnosis can often be made on patients admitted for other complaints, before the subjective symptoms are sufficiently developed to send them to nervous and mental specialists or to insane hospitals. In the medical department of the University Hospital routine spinal punctures are done, not only on the nervous and mental patients, but also in any cases showing signs of syphilis or in which a definite diagnosis cannot be made. Therefore, with this material at hand, there was undertaken a study of the colloidal gold reaction, consisting of the technic of the test, a résumé of previous literature, and an interpretation of the "curves" based on these clinical and laboratory data.

First of all, in the study of any test, one must consider the allied reactions.[1] For globulin the Nonne test was most commonly used. This is done by mixing equal parts of supersaturated ammonium sulphate solution and spinal fluid. A white cloud or opalescence appearing in three minutes means an increase of globulin. In common with

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1. The Wassermann tests were done in the department of bacteriology under the supervision of Dr. W. P. Larson. All the other reactions were performed by one of us.

Lee[2] and Hinton[3] we have had difficulty with this reaction, first due to hyposaturation, and later to an accidental substitution of magnesium for ammonium sulphate. Following the correction of these errors the test has been very satisfactory. More recently the Ross-Jones[4] ring test, a modification of the Nonne,[5] has also been employed. This consists of layering 1 c.c. of spinal fluid on 1 or 2 c.c. of a supersaturated solution of ammonium sulphate. A white or gray ring marking the point of contact of the two fluids constitutes a positive reaction. This has proved in our hands to be the most satisfactory globulin test. It is sharp, clear cut, easily read, and not often confused with a slightly opaque containing tube as is the Nonne. For some time the Pandy[6] reaction was employed in conjunction with the others, but was found to have no advantage over the Ross-Jones test, except that smaller amounts of spinal fluid might be used, and it has the disadvantage of being so sensitive that apparently positive results are frequently obtained, unconfirmed by other positive tests. Its technic consists of dropping one drop of spinal fluid into 1 or 2 c.c. of a saturated solution of phenol. The immediate appearance of a bluish white cloud signifies an increased globulin content.

For the cell count Alzheimer's method was not deemed feasible. Consisting as it does of celloidin embedding and sectioning of the centrifuged cells, it is of value only as a means of careful study and differential count of the individual cells, and is absolutely useless for a total count. From the point of view of both labor and time involved it is impractical for the routine laboratory worker. The method used in our laboratory is that described by Swift and Ellis[8] in which an ordinary counting chamber and pipet, such as is used for the counting of leukocytes, was employed. The diluting fluid consists of 10 per cent. acetic acid with about 1 per cent. of methyl violet to stain the leukocytes to distinguish them from the erythrocytes, and to make a differential count possible in the same preparation. This strength of acetic acid is sufficient to hemolyze the majority of the erythrocytes which may be present. The diluting fluid is drawn to the mark 1, then the spinal fluid is drawn to the mark 11, thus giving a very low dilu-

2. Lee: A Simple Procedure for the Preparation of Colloidal Gold for Diagnostic Purposes, Am. J. M. Sc. **155**:404, 1918.

3. Lee and Hinton: A Critical Study of Lange's Colloidal Gold Reaction in Cerebrospinal Fluid, Am. J. M. Sc. **148**:33, 1914.

4. Ross: On the Use of Certain New Chemical Tests in the Diagnosis of General Paralysis and Tabes, Brit. M. J. **1**:1111, 1909.

5. Nonne: Syphilis und Nervensystem, Ed. 2, **105**: Berlin, 1909.

6. Pandy: Ueber eine neue Eweissprobe für die Cerebrospinalflüssigkeit, Neurol. Centralbl. **29**:915, 1910.

7. Alzheimer: Einige Methoden zur Fixierung der zelligen Elemente der Cerebrospinalflüssigkeit, Centralbl. f. Nervenh. u. Psychiat. **6**:15, 1907.

8. Swift and Ellis: Cerebrospinal Fluid in Syphilis, J. Exp. M. **18**:162, 1913.

tion. As the cells of a normal fluid, at least, are few in number, it is best to count the whole nine square millimeters of the field, the number thus obtained being divided by nine to give the average per square millimeter, multiplied by ten to get the number in 1 c.mm., and finally by 10/9 for the dilution. In other words, we use the following equation, the number of cells in the whole field being represented by X:

$$X \times 10/9 \times 10/9 = 100/81X, \text{ or, roughly, } 1\ 1/5X$$

The Fuchs-Rosenthal[9] chamber has no advantage over the one mentioned above and is not as desirable for the ordinary laboratory, as it cannot be used for other purposes. All cell counts done by us were made as soon as possible after the puncture was done, but the error on standing is not as great as is generally supposed. Our experience has been that if the fluid be well shaken each time, the count will remain the same for from six to eight hours. Without the shaking, however, especially if the pipet be filled from the bottom of the tube, the count rises slowly, pointing to the fact that the cells readily sink to the bottom rather than cling to the sides of their containing tube, as suggested by Swift and Ellis.

But it is in the preparation of the colloidal gold solution that every laboratory worker, whether amateur or experienced, comes to grief sooner or later. Most authors agree that a constant standard solution cannot always be made, and that skill consists in ability to recognize and remedy the faulty solution. After months of success one is sometimes suddenly confronted by a so-called "protected solution" or more rarely a hyperactive solution which gives the right curve but produces it with unusual rapidity and exaggerated color changes. However, there are almost as many suggestions for improvement of the method as there are writers on the subject, Glaser[10] being the exception in believing that it could never be made satisfactory. Lange,[11] Eicke,[12] Grulee and Moody,[13] Jaeger and Goldstein,[14] Kaplan and McClelland,[15]

9. Fuchs and Rosenthal: Physikalischchemische zytologische und anderweitige Untersuchungen der Cerebrospinalflüssigkeit, Wien. med. Presse **14**: 2135, 2242, 2190, 1904.

10. Glaser: Zur klinischen Brauchbarkeit der Lange'schen Goldsolreaktion in der Psychiatrie, Neurol. Centralbl. **33**:688, 1914.

11. Lange: Die Ausflockung kolloidalen Goldes durch Cerebrospinalflüssigkeit bei leutischen Affektionen des Zentralnervensystem, Ztschr. f. Chemotherap. **1**:44, 1912.

12. Eicke: Die Goldreaktion im Liquor cerebrospinalis, München. med. Wchnschr. **60**:2713 1913.

13. Grulee and Moody: Lange's Gold Chloride Test on the Cerebrospinal Fluid in Congenital Lues, J. A. M. A. **61**:13 (July 2) 1913. Grulee and Moody: The Lange Gold Chloride Reaction on the Cerebrospinal Fluid of Infants and Young Children, Am. J. Dis. Child. **9**:17 (Jan.) 1915.

14. Jaeger and Goldstein: Goldsolreaktion im Liquor cerebrospinalis, Ztschr. f. d. ges. Neurol. u. Psychiat. **16**:219, 1913.

15. Kaplan and McClelland: The Precipitation of Colloidal Gold, J. A. M. A. **62**:511 (Feb. 14) 1914.

Flesch,[16] Lee and Hinton,[3] Miller and Levy,[17] Eskuchen,[18] Hammes[19] and Felton,[20] Harvey,[21] Kolmer,[22] Hulbert,[23] Speidel and Smith[24] all advocate their own methods or modifications which they find satisfactory. All authors agree, however, on certain essentials for a successful solution. These are (1) perfectly clean, hard Jena glassware; (2) water freshly double — or preferably triple — distilled in a glass still having no rubber connections; (3) chemically pure reagents, dissolved in the water mentioned above. The methods suggested for cleaning the glassware are many and include boiling with strong soap and water, washing with potassium bichromate or aqua regia, and followed by thorough rinsing in tap water. Our most satisfactory results have been obtained by rinsing all glass utensils with equal parts of concentrated hydrochloric and nitric acids, taking care that no small area on the inner surface escapes the process. They are then placed under running tap water until all the acid is removed. This is then followed by a rinsing with, first, ordinary distilled water, and then with distilled spring water. If this procedure is carried out on new glassware it need not be repeated as long as the utensils are reserved for this use only, as simply rinsing them in distilled spring water cleanses them sufficiently for use. During the past few months Jena glass has not been obtainable, but American made glass has served as well.

For the preparation of the reagent, 2,000 c.c. flasks, either the Erlenmeyer or round bottomed, are found to be more satisfactory and more easily handled than beakers. In addition one needs one 10 c.c. pipet graduated in 1 c.c. and a 1 c.c. pipet graduated in $\frac{1}{10}$ c.c. In our experience the distilling of the water is the most important factor determining success or failure in making the solution. Any of the reagents if dissolved in improperly distilled water will spoil any solution for which they are used even if the bulk of the water be

16. Flesch: Die Untersuchung des Liquor cerebrospinalis mit kolloidalen Goldlösung, Ztschr. f. d. ges. Neurol. u. Psychiat. **26**:318, 1914.
17. Miller and Levy: The Colloidal Gold Reaction in Cerebrospinal Fluid, Bull. Johns Hopkins Hosp. **25**:133, 1914.
18. Eskuchen: Die fünfte Reaktion, Ztschr. f. d. ges. Neurol. u. Psychiat. **25**:486, 1914.
19. Hammes: The Comparative Value of the Wassermann, the Colloidal Gold and Other Spinal Fluid Tests, Am. J. M. Sc. **154**:625, 1917.
20. Felton: Cerebrospinal Fluid and the Colloidal Gold Test, New York M. J. **105**:1170, 1917.
21. Harvey: The Colloidal Gold Test in Diagnosis, California State J. M. **16**:170, 1918.
22. Kolmer: Infection, Immunity and Serum Therapy, Ed. 2, 1917, p. 437.
23. Hulbert: Technical Improvement in Lange's Colloidal Gold Test, J. Mich. M. S. **15**:30, 1916.
24. Speidel and Smith: The Preparation of Colloidal Gold, U. S. Nav. M. Bull. **12**:220, 1918.

satisfactory. Frequent distillations of our tap water failed to give water which would produce a proper solution, probably because of the chlorites added for the purpose of purification, which allowed volatile chlorin to come over into each freshly distilled solution. On the other hand, single distillation of spring water sold for drinking purposes gave perfect results. All of the difficulties of preparation (usually resulting in the so-called "protected" solution) in our laboratory have been traceable directly to the water. A similar idea as to the importance of properly distilled water is held by Black, Rosenberg and McBride,[25] but in addition they also place great stress on slow regular heating, while in our hands the mode of heating was found to be of little significance, the use of one small Bunsen flame giving just as satisfactory results as a powerful three-flame burner or the two used alternately on the same solution.

All solutions of our reagents were kept in stock, and were made from Merck products and distilled spring water. The only method ever employed here is that of Miller, Brush, Hammers and Felton.[26] One thousand c.c. of distilled spring water was heated slowly in a 2,000 c.c. flask to 50 C., then rapidly to 60 C., when 10 c.c. of a 1 per cent. solution of gold chlorid and 7 c.c. of a 2 per cent. solution of potassium carbonate were added. At 80 C., 10 drops of a 1 per cent. solution of oxalic acid were added. At 90 C. the flask was removed from the flame and slowly, drop by drop, 5 c.c. of a 1 per cent. solution of liquor formaldehydi was put in. The flask was then shaken until there appeared a pink color, slowly changing to a violet and then to a deep dark red, clear to both direct and transmitted light, and occasionally with a slight golden shimmer. In addition to having the proper color, this solution, when set up in the ordinary manner, must also remain unchanged when run with a known normal spinal fluid; give a typical curve with a known paretic fluid; 5 c.c. of it must be completely precipitated in one hour by 1.7 c.c. of 1 per cent. solution of sodium chlorid; and, most important of all, must be neutral to a 1 per cent. solution of alizarin red in 50 per cent. alcohol. The laboratory worker of today is deeply indebted to Miller and his associates for working out the method of determining the reaction of the solution and making it possible to correct each faulty one instead of frequently discarding large amounts.

The technic for testing the neutrality of the solution is very simple. To 5 c.c. of the solution in a test tube are added 2 or 3 drops of alizarin

25. Black, Rosenberg and McBride: The Colloidal Gold Test, J. A. M. A. **69**:1855 (Dec. 1) 1917.

26. Miller, Brush, Hammers and Felton: A Further Study of the Diagnostic Value of the Colloidal Gold Reaction Together with a Method for the Preparation of the Reagent, Bull. Johns Hopkins Hosp. **26**:391, 1915.

red as indicator. From this it is determined whether an acid or an alkali is needed to bring it to the neutral point. Ten clean test tubes are set up in a rack, and to each is added 1 c.c. of distilled spring water. To the first tube is added 1 c.c. of fiftieth normal hydrochloric acid or sodium hydroxid, as the case may be, thus giving 0.5 c.c. hydrochloric acid or sodium hydroxid. From this first tube 1 c.c. is transferred to the 1 c.c. of water in the second tube, giving 0.25 c.c. of the acid or alkali, and so on until the tenth tube contains only 0.0009765625 c.c. of the acid or alkali. Then, to each tube are added two drops of alizarin red and 5 c.c. of colloidal gold. The color changes from canary yellow in the acid, brownish red in the neutral, deep dark red in the faintly alkaline, to a deep purple in the strongly alkaline solution. The tube showing the most typical brownish red is selected as the neutral; the amount of acid or alkali in that tube is divided by five to determine the amount necessary to neutralize 1 c.c.; this is multiplied by the number of cubic centimeters to be corrected and the resulting amount of the fiftieth normal hydrochloric acid or sodium hydroxid added to the solution, which is then ready for use. The only point which may prove confusing to the amateur is the fact, not made clear in the literature, that a deep dark red with a purplish tinge in the upper layers when shaken, as well as the deep purple, is a definite sign of an alkaline solution, and that no red without a definite brownish tinge should be regarded as neutral.

Craig[27] suggests placing 10 c.c. of colloidal gold solution and from three to four drops of the indicator in a glass beaker and titrating with the acid or alkali until the neutral point is reached. But with such a confusing play of reds, browns and purples merging into each other it is practically impossible to recognize and stop at the neutral point, while in the method given above one may observe side by side the different color shades as brought about by the various dilutions and get a much more clear cut picture of the neutral point.

After a satisfactory solution is once obtained, it appears to be very stable, and if kept corked in a dark cupboard will remain satisfactory for months. The fine black precipitate or even the surface mold which occasionally appears in warm weather will not interfere with the reaction.

A so-called "protected" solution, reacting neither to 1 per cent. sodium chlorid nor to a known positive fluid, is usually alkaline. Felton[20] considers that such a solution is due to an unusually wide distribution of the colloidal particles from slow or irregular heating. We have found correct the observation of Craig that alkaline solutions are inert with a positive spinal fluid; slightly acid solutions will react

27. Craig: The Wassermann Test, 1918, p. 213.

as usual with paretic fluids, but with normal fluids will also give a curve similar to that of syphilis, while a strongly acid solution will give very little reaction with a positive fluid, but will show an abnormal reaction with normal fluids. Therefore, we agree with the majority of authors that a neutral solution is of the most vital importance. Moody[28] with ordinary precautions always obtains a neutral solution. Lee,[2] in contradistinction to practically all other observers, prepares his solutions with ordinary distilled water with no regard to age or method, uses only ordinary laboratory cleansing methods for his glassware, adds all reagents, except liquor formaldehydi, at once; pays no attention to neutrality, yet claims perfect results with all his solutions. But in our hands, as with most workers, a much more refined and careful technic seems necessary for satisfactory solutions and reactions.

The technic of setting up the test is very simple. Eleven clean test tubes are set up in a rack and to each is added 1 c.c. of a 0.4 per cent. sodium chlorid solution. In the first tube is placed in addition 0.8 c.c. of the salt and 0.2 c.c. of spinal fluid, making 2 c.c. of a 1:10 dilution. From this tube 1 c.c. is removed and added to the 1 c.c. of salt in the second tube, making a dilution of 1:20. This is continued to the tenth tube which has a dilution of 1:5,120 and the last 1 c.c. of this dilution is discarded. Then add to each tube 5 c.c. of the colloidal gold solution and shake the tube well to facilitate mixture. The eleventh tube, therefore, contains only sodium chlorid and colloidal gold and serves as a control. The 4 per cent. sodium chlorid may be kept as a stock solution instead of diluting a 10 per cent. solution each time, as given in Lange's early technic. We have also found that this solution will prove just as satisfactory made up with ordinary distilled water as with double or triple distilled water.

A positive reaction, if present at all, begins to appear at once and then intensifies for several hours, being complete in from eight to twelve hours. As Solomon and Welles[29] have mentioned, all syphilitic curves appear the same at first with a "paretic" one developing later, and are only complete after twelve hours, so that if read too early a paretic curve may be confused with a syphilitic one. On the other hand, a test showing no beginning color changes at the end of one-half hour may as well be discarded, as none will appear later. For our readings we designate an unchanged fluid as 0; a bluish red as 1; a reddish blue as 2; a deep blue as 3; a gray blue as 4, and colorless as 5.

28. Moody: Discussion, New York M. J. **105**:1170, 1917.

29. Solomon and Welles: Varieties of Gold Sol Test in Several Loci of the Cerebrospinal Fluid System, Boston M. & S. **172**:625, 1915; The Development of the Gold Sol Paretic Reaction as Compared with the Cerebrospinal Meningitis Type Considered from the Time Necessary to Form a Complete Reaction, ibid. **174**:50, 1916; On the Value of the Gold Sol Test in Cerebrospinal Fluid Obtained Postmortem, ibid. **172**:398, 1915.

Because of the peculiar shades all readings must be done with direct daylight, holding the tubes up against the sky instead of against green grass or colored buildings.

The so-called typical "paretic" curve shows the first few tubes completely precipitated, giving a colorless solution, while lesser changes may appear in the remaining ones, e. g., 5555543000. The syphilitic curve shows the first one or two tubes unchanged with the maximum color change (which is usually 3, seldom beyond 4) in the fourth or fifth tube, as 0023311000. This includes the curves of both tabes and cerebrospinal syphilis, as this reaction does not differentiate between them. The so-called "meningitic" curve which does not distinguish between different types of meningitis or myelitis is designated by the early writers as "verschiebung nach oben," and consists of a curve showing color change in the right half of the tubes with the maximum reaction in the seventh or eighth, as 0000013310. Because of the possible nonsyphilitic causes, such as multiple sclerosis, of these zonal reactions, Felton and Maxy[30] make the timely suggestion of designating these zones by roman numerals rather than by terms, such as "paretic" or "syphilitic" curves. Thus, they call tubes with a maximum reaction and complete precipitation of from 1:10 to 1:160, zone I; those showing a reaction up to 4 and including dilutions of from 1:40 to 1:160 as zone II; and those showing the maximum color change beyond 1:160 as zone III.

It is of interest to note the attitude toward this reaction of the authors who employed it during the trial period. Lange concluded that the test was of importance in early diagnosis leading to early treatment, thereby preventing or modifying severe syphilitic and "metasyphilitic" diseases of the central nervous system. Jaeger and Goldstein obtained charactertistic curves in 100 per cent. of cases of cerebrospinal syphilis and paresis. Swift and Ellis, among the earlier workers in this country, used it in a few cases and concluded that it was no more delicate than the Noguchi butyric acid test. Glasor felt that it was of no practical value because of the difficulty in preparing a satisfactory reagent. Kafka[31] found difficulty in differentiating between cerebrospinal syphilis and paresis, but still considered it the most important of all spinal fluid tests. Sippy and Moody[32] found it

30. Felton and Maxy: The Colloidal Gold Reaction in the Cerebrospinal Fluid in Acute Poliomyelitis, J. A. M. A. **68**:752 (March 10) 1917.

31. Kafka: Ueber die Bedeutung der Goldsolreaktion der Spinalflüssigkeit zur Erkennung der Lues des Zentralnervensystems, Dermat. Wchnschr. **58**: 52, 1914. Kafka: Ueber den heutigen Stand der Liquor diagnostic, München. med. Wchnschr. **62**:105, 1915.

32. Sippy and Moody: The Colloidal Gold Reaction in the Diagnosis of Syphilitic and Other Lesions of the Central Nervous System, Trans. Assn. Am. Physicians **28**:720, 1913.

more sensitive and more exact than the Wassermann test and of especial value in differentiating between the various syphilitic diseases. Eicke noted a parallelism between the colloidal gold curve and lymphocytosis. Eskuchen found it to be of decided value not only in conjunction with other tests, but also independently. Solomon and Koefod[33] considered it of great value as a diagnostic aid, but thought a "syphilitic curve" did not indicate syphilis unless supported by a positive Wassermann test. Weston, Darling and Newcomb[34] considered the reaction a valuable addition to the Wassermann test, but found a few nonsyphilitic cases giving a "syphilitic curve." Lee and Hinton decided that the test did not parallel the others, but was usually corroborated by one other test, and also was more sensitive than the Wassermann. Kaplan and McClelland obtained typical curves for all paretics and most tabetics, but not in all cases of cerebrospinal syphilis. Flesch thought it more delicate and clear cut than the other tests. Miller and Levy recognized the great value of the reaction, but pointed out that it did not differentiate between purulent and tuberculous meningitis, was inconstant in secondary and tertiary lues, and was useless in congenital syphilis. Barnes and Ives[35] consider it of value when used with other tests even though they find that there is no characteristic curve differentiating tabes from cerebrospinal syphilis, that negative curves do not exclude syphilis and that, while it parallels other tests rather closely, yet it is not more delicate. Solomon, Koefod and Welles[36] decided that the reaction was of the greatest value and should complete every spinal fluid examination, but that a positive reaction did not indicate syphilis unless supported by other tests. Swalm and Mann[37] found no curves in their study of nonsyphilitic psychoses, yet did not always find the test specific for syphilis. Miller and his associates felt that this reaction, while not replacing the other tests, has a sensitiveness and specificity not shared by the others; that the sources of error are few and easily recognized, and that the results are clear cut and decisive. Solomon and Southard[38] found it to be

33. Solomon and Koefod: Experience with Lange's Colloidal Gold Test in 135 Spinal Fluids, Boston M. & S. **171**:886, 1914; Significance of Changes in Cellular Content of Cerebrospinal Fluid in Neurosyphilis, ibid. **173**:996, 1915.

34. Weston, Darling and Newcomb: The Colloidal Gold and Other Tests Applied to the Spinal Fluid in Psychiatry, Am. J. Insan. **71**:773, 1914.

35. Barnes and Ives: The Cerebrospinal Fluid in Syphilis of the Central Nervous System with Special Reference to Lange's Colloidal Gold Reaction. Interstate M. J. **22**:792, 1915.

36. Solomon, Koefod and Welles: The Diagnostic Value of Lange's Gold Sol Test, Boston M. & S. J. **173**:957, 1915.

37. Swalm and Mann: The Colloidal Gold Test on Spinal Fluid in Paresis and Other Mental Diseases, New York M. J. **101**:719, 1915.

38. Solomon and Southard: Notes on Gold Sol Diagnostic Work in Neurosyphilis, J. Nerv. & Ment. Dis. **45**:230, 1917.

of as much value on postmortem as antemortem fluids. Hammes[39] thought that the colloidal gold test was more delicate than any other test and usually did not react with a negative fluid yet should be used in conjunction with the other tests. Black, Rosenberg and McBride did not find this reaction appearing after provocative treatment, yet considered it to be the first of the reactions to appear in the development of the disease. Lowrey[39] found it of immense value with, however, atypical positive curves in 10 per cent. and decided atypical curves in 10 per cent. more, yet no positive reactions with nonsyphilitic cases. Harvey noted this test occasionally occurring alone in cerebrospinal syphilis and tabes. He considered it of great value; nevertheless, he thought it should not replace the other tests. Vogel[40] considered it of special value in tabes, but found a few syphilitic curves occurring in neurasthenia, "serous" meningitis, hemiplegias and chronic alcoholism. Weston[41] raises the question of a positive reaction always indicating syphilis and reports three cases with paretic curves not accompanied by a history of syphilis, positive Wassermann, or luetin test. Craig thought it the most valuable of all confirmatory evidence. Rawlings,[42] while recognizing the importance of the colloidal gold reaction in general, considered it of especial value in differentiating between syphilitic and senile arteriosclerotic cases. In her experience the cases in which necropsies showed syphilitic vascular lesions had shown syphilitic curves, while those of simple senile degeneration had shown negative reactions.

### CLINICAL INTERPRETATION

In the following analysis of over 800 spinal fluids from 408 patients we have grouped the cases, for purpose of study, under the following divisions: (1) dementia paralytica, (2) tabes dorsalis, (3) cerebrospinal syphilis, (4) multiple sclerosis, (5) cord and brain tumors, (6) meningitis, (7) miscellaneous.

Spinal punctures are done practically as a part of the routine examination on patients on the nervous and mental service and, also, in all medical cases presenting any evidence of involvement of the nervous system. The diagnoses and laboratory findings were tabulated from the patients' clinical records.

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39. Lowrey: Cerebrospinal Fluid Tests, Especially the Gold Reaction, in Psychiatric Diagnosis, J. Nerv. & Ment. Dis. **46**:186, 1917.
40. Vogel: The Nature and Interpretation of the Colloidal Gold Reaction, Arch. Int. Med. **22**:496 (Oct.) 1918.
41. Weston: Does a Colloidal Curve Indicate Syphilis? Am. J. Insan. **74**: 431, 1918; The Colloidal Gold Precipitating Substance in the Cerebrospinal Fluid in Paresis, J. M. Research **34**:107, 1916; The Colloidal Gold Reaction, Am. J. Syph. **3**:266, 1919.
42. Rawlings: Colloidal Gold Reaction in 498 Psychiatric Cases, Arch. Neurol. & Psychiat. **2**:180, 1919.

The final diagnosis is made by the clinician at the time the patient leaves the hospital. He has the complete clinical and laboratory record before him, and, if a diagnosis of a syphilitic lesion of the nervous system is made when the laboratory tests are partially or completely negative, it is because the attending physician believes the clinical evidence justifies such a conclusion in spite of the lack of corroboration by biologic reactions.

In the summary of the tables under each heading in our discussion the figures represent the number of cases and percentages. Cell counts of five and less are called "negative," and cells counts of more than five are "positive." The sign "±" refers to reactions that are "slightly" or "faintly" positive, and if unaccompanied by other positive findings are ordinarily regarded as of no significance; this is especially true of the Nonne test.

### DEMENTIA PARALYTICA

The value of the colloidal gold reaction in paresis is well recognized. It is rarely negative in untreated cases and commonly gives a curve in zone I. A reduction, at least in zone II, tends to persist even when the patient is receiving intensive treatment.

TABLE 1.—RESULTS OF EXAMINATION OF CEREBROSPINAL FLUID BY MEANS OF NONNE, COLLOIDAL GOLD AND WASSERMAN TESTS IN DEMENTIA PARALYTICA

| | Nonne | Cells | Colloidal Gold | Cerebrospinal Fluid Wassermann |
|---|---|---|---|---|
| Total cases | 19 | 19 | 18 | 18 |
| + | 14 = 73.68% | 13 = 68.42% | 17 = 94.5% | 15 = 83.30% |
| ± | 2 = 10.52% | | | |
| − | 3 = 15.78% | 6 = 31.57% | 1 = 5.5% | 3 = 16.66% |

In fifteen of the eighteen cases marked reactions were noted in zone I; in other words, a "paretic" curve. The one patient whose fluid was negative, except for a positive Wassermann, had received much treatment. Many authors have mentioned occasional nonsyphilitic cases, other than multiple sclerosis, which gave typical paretic curves. One such in our series (Case 16249), a case of brain abscess verified by operation, gave on two separate punctures a curve in zone I unsupported by other positive laboratory findings.

### TABES DORSALIS

Of the spinal fluid reactions in tabes dorsalis, the colloidal gold is definitely the most valuable. In nine instances it was positive when the other tests were negative, and in seven other cases it was present with only one other positive reaction. If cell counts of nine and below

had been accepted as normal there would be only twenty cases, or 29.8 per cent., in which the cell count was "positive." Well marked curves were found in fairly early cases. In several patients given provocative treatment after one or more examinations had shown the fluid to be entirely negative we found the colloidal gold reaction to be the first to appear. In patients with a questionable clinical diagnosis of syphilis of the nervous system and whose spinal fluid is entirely negative, it is well worth while to give antisyphilitic treatment for three or four weeks and then to repeat the laboratory examinations at least twice with a week's interval between.

TABLE 2.—General Paresis

| Hospital No. | Nonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|
| 9478 | + | 29 | 5532211000 | + |
| 8497 | + | 26 | | |
| 8589 | + | 20 | 5555444322 | + |
| 12625 | + | 20 | 5555430000 | + |
| 14031 | + | 50 | 5555222211 | + |
| 14168 | ± | 5 | 4555322000 | + |
| 14328 | + | 40 | 5555433200 | + |
| 14401 | ± | 5 | 255333100 | + |
| 14140 | — | 2 | — | + (history, much treatment) |
| 16189 | + | 5 | 0122311000 | — early ? |
| H. | .. | .. | 1122333100 | |
| M. | + | 281 | 4444311000 | + |
| 16902 | ++ | 60 | 5555554100 | + |
| P. | + | 10 | 5555555100 | — |
| 9215 | + | 11 | 5554220000 | + |
| 12391 | + | 25 | 5554422000 | + |
| 12296 | — | 1 | 4442200000 | — |
| 9802 | + | 27 | 4443332000 | + |
| 16305 | — | 4 | 5544422000 | + |
| 16841 | ++ | 75 | 5555555530 | + |

TABLE 3.—Tabes Dorsalis

| | Nonne | Cells | Colloidal Gold | Cerebrospinal Fluid Wassermann |
|---|---|---|---|---|
| Total cases | 71 | 67 | 74 | 72 |
| + | 31 = 43.79% | 29(6+) = 46.3% | 55 = 74.3% | 38 = 52.6% |
| ± | 14 = 19.7% | | 4 = 5.4% | |
| — | 26 = 37% | 38(—5) = 53.7% Aver. = 16.3% | 14 = 18.9% | 34 = 47.3% |

The cases that were diagnosed as tabes dorsalis in spite of negative spinal fluid reactions presented, as a rule, well marked signs and symptoms of the disease. One case (Case 16916) illustrates this very well. The patient gave a history of gonorrhea and a probable chancre eighteen years before; he complained of a swollen knee, girdle sensation, sphincteric and gastric disturbances. Physical examination showed Argyll Robertson pupils, incoordination, loss of deep pain sense in the calves and tendo Achilles, impaired sensation over the nose and across the chest, marked hypertonia, lost knee jerk on one

TABLE 4.—Tabes Dorsalis

| Hospital No. | Nonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|
| 9183 | .. | .. | 1123321000 | + |
| 9436 | ± | 21 | — | — (Cerebrospinal syphilis) |
| 9530 | ± | 1 | — | — |
| 9726 | ± | 48 | 5443330000 | + (50%) |
| 9987 | + | 22 | 122221000 | + |
| 9183 | .. | 1 | 1123321000 | + |
| 8876 | .. | 7 | 5544421000 | + |
| 7955 | + | 7 | 0124321100 | + |
| 7727 | ± | 7 | 2233333200 | + |
| 8404 | — | 1 | — | — |
| 11582 | — | 1 | — | — (much treatment) |
| 12611 | ± | 1 | 223332000 | + |
| 12753 | — | 1 | — | — |
| 12309 | — | 1 | — | — |
| 12511 | + | 80 | 4555555544 | + |
| 12056 | ± | 6 | 1123100000 | + |
| 10752 | — | 0 | — | + |
| 10977 | ± | 5 | 223332000 | + |
| 11018 | + | 15 | 222332000 | + |
| 10681 | + | 5 | 222322000 | + |
| 12956 | + | 22 | 222332000 | + |
| 12831 | + | 3 | 1113320000 | + |
| 13068 | + | 30 | 1133332000 | + |
| 12753 | — | 1 | — | — |
| 13342 | + | 125 | 1123210000 | + |
| 14441 | — | ? | 1112311000 | + |
| 10933 | ± | 2 | 012311000 | — |
| 10367 | ± | 3 | 001232000 | — |
| 14470 | — | 2 | 001233321 | — |
| 10552 | + | 5 | 0013321000 | |
| 13000 | + | 15 | 2223100000 | + |
| 14257 | + | 250 | 2223442100 | + |
| 14442 | — | 1 | — | — |
| 10215 | + | 5 | 5555542200 | —? |
| 10797 | + | ? | 0023332100 | — |
| 12627 | ± | 24 | 1133320000 | + |
| 12966 | + | 3 | 4433321000 | + |
| 13016 | + | 36 | 1122332100 | + |
| 14201 | — | 1 | — | — |
| 14474 | — | 2 | — | — |
| 14521 | + ft. | 3 | 1122330000 | + |
| 14491 | + | 80 | 1112311000 | + |
| 14636 | — | 2 | — | — Treated |
| 14857 | — | 1 | — | — |
| 14512 | — | 2 | 0031100000 | + |
| 15857 | — | 21 | 2233320000 | + |
| 15095 | ± | 8 | 1223331000 | + |
| 15808 | + | 10 | 1223210000 | + |
| 15095 | .. | .. | 2233332000 | + |
| S. | + | 10 | 0001121000 | + |
| B. | — | 1 | 0012321 | — |
| A. N. | — | 1 | 0002100000 | — |
| N. | ± | 3 | 0013332000 | — |
| W. | + | 30 | 0013100000 | — |
| 16137 | — | 1 | — | — |
| K. | — | 4 | 0012210000 | — |
| B. | + | 20 | 0123332000 | + |
| S. | + | 3 | 0012210000 | — |
| F. | — | 20 | 1233210000 | + |
| H. | + | 25 | 455554200 | + |
| A. J. | — | 1 | 2223310000 | — |
| B. | ± | 2 | 1122210000 | — |
| C. | — | 6 | 0000111233 | — |
| 16386 | — | 2 | 0013220000 | — |
| McQ. | + | 5 | 0113320000 | — |
| 16495 | — | 45 | 0123334100 | + |
| 16656 | — | 12 | 0013331000 | + |
| 15549 | ± | 2 | 4433332100 | + |
| 14470 | — | 2 | 0012332100 | — |
| 16393 | — | 3 | — | — |
| 16843 | ± | 1 | 0012311000 | — |
| 16840 | ++ | 45 | 0225555551 | + (also pachymeningitis) |
| C. | + | ? | 0013441000 | — |

side, and a typical Charcot joint of the other knee. Six spinal fluids all from different punctures were entirely negative. The blood Wassermann, however, was always positive in this case.

### CEREBROSPINAL SYPHILIS

The value of the colloidal gold test is strikingly shown in the series of cases of cerebrospinal syphilis. Eighty-five per cent. of the fluids gave some reduction, and 75 per cent. definite curves. On the other hand, the Nonne was positive in 63 per cent., and definitely positive in only 31 per cent.; there was a cell count above five in 45 per cent., and above nine in only 31 per cent. The Wassermann was positive in 48 per cent. In 18 per cent. of the cases the colloidal gold was the only reaction that gave evidence of a pathologic condition of the cerebrospinal fluid. The fluids from cases of cerebrospinal syphilis tend to give a reduction in zone I, somewhat more frequently than those from cases of tabes dorsalis. It has been suggested by Solomon and Welles that the curve of cerebrospinal syphilis is a "forme fruste" of the curve commonly found in dementia paralytica.

TABLE 5.—CEREBROSPINAL SYPHILIS

| | Nonne | Cells | Colloidal Gold | Cerebrospinal Fluid Wassermann |
|---|---|---|---|---|
| Total cases | 27 | 27 | 27 | 27 |
| + | 11 = 40.74% | 12 = 44.44% | 21 = 77.79% | 13 = 48.14% |
| ± | 6 = 22.22% | | 2 = 7.4% | |
| − | 10 = 37.03% | *15 = 55.55% | 4 = 14.8% | 14 = 51.85% |

* If cell counts below ten are regarded as normal, then there were only nine positive cell counts or only 31 per cent.

### MULTIPLE SCLEROSIS

Miller, Brush, Hammer and Felton reported three cases of disseminated sclerosis, all giving "paretic" curves. Hammes examined the fluid in four cases and only one gave the curve of paresis. Flesch found a "paretic" curve in six out of eight cases. Kaplan[43] saw such a curve only once in eighteen cases. Oetiker[44] obtained a reduction of the colloidal gold in one case. Kaplan and McClelland, Vogel, De Crinis and Frank[45] each reported two cases giving one paretic and one syphilitic curve. Craig found the results in multiple sclerosis to be indefinite. Solomon and Koefod reported four cases; two gave a "paretic" curve; one a "syphilitic" curve, and one was negative.

43. Kaplan: General Paresis, New York M. J. **100**:397, 1914.
44. Oetiker: Erfahrungen mit der Langeschen gold sol Reaktion im Liquor cerebrospinalis, Ztschr. f. klin. Med. **82**:235, 1915.
45. De Crinis and Frank: Ueber die Goldsol reaktion im Liquor cerebrospinalis, München. med. Wchnschr. **61**:1216, 1914.

Solomon and Southard suggest that the positive colloidal gold reductions in these cases may be due to the substance produced in the process of atrophy and sclerosis. Of the conditions other than syphilis and meningitis giving a well marked curve, multiple sclerosis is the one most frequently met. While often emphasized that the curve in disseminated sclerosis resembles that of paresis, it is our experience that the curve is more frequently in zone II, as is illustrated by the fact that nine of our twenty-two cases gave curves of this type, while only two cases were in zone I. The finding of an average cell count of 14 in multiple sclerosis as against the average of 1.6 in normal fluids is interesting in that it tends to confirm the theory of a toxic etiology in this disease.

TABLE 6.—CEREBROSPINAL SYPHILIS

| Hospital No. | Nonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|
| 14203 | + | 300 | 5555443311 | + |
| 14408 | — | 10 | 0002232100 | + |
| 13946 | + | 18 | — | — |
| 14143 | — | 1 | — | — |
| 14177 | — | 1 | — | — (20 arsphenamin treatments, much Hg.) |
| 12878 | + | 12 | 2223322000 | + |
| 8512 | ± | 1 | 1112333210 | + |
| 7796 | — | 1 | 0122210000 | — |
| 8081 | + | 70 | 2555443321 | + |
| 8607 | ± | 170 | 2222211100 | + |
| 12114 | + | 1 | 0343332200 | + |
| 14140 | — | 1 | — | — |
| 10393 | + | 12 | 0112333000 | — |
| 80367 | ± | 3 | 0012330000 | — |
| 12680 | ± | 1 | 1112220000 | — |
| 9218 | — | 1 | 0013321000 | — |
| 14444 | + | 50 | 4222200000 | + |
| 14408 | — | 9 | 0002232100 | + |
| 14833 | — | 1 | 0002332100 | — |
| 15858 | — | 1 | 0001232000 | + |
| 15000 | — | 6 | 0012221000 | — |
| 16159 | + | 235 | 2444333211 | + |
| 15847 | ± | 2 | 4433332100 | + |
| 16850 | + | 1 | 0012200000 | + |
| 16847 | + | 1 | 0123331000 | — |
| 16890 | ± | 9 | 0144442000 | — |

TABLE 7.—MULTIPLE SCLEROSIS

| | Nonne | Cells | Colloidal Gold | Cerebrospinal Fluid Wassermann |
|---|---|---|---|---|
| Total cases | 21 | 20 | 20 | 21 |
| + | 2 = 9.52% | 7 = 35% | 9 = 45% | |
| ± | 4 = 19.04% | | 2 = 10% | |
| — | 15 = 71.42% | 13 = 65% | 9 = 35% | 21 = 100% |

BRAIN AND SPINAL CORD TUMORS

Although generally overlooked in the literature, we feel that a curve in zone III, especially unaccompanied by meningitic symptoms, is of very definite diagnostic value as indicating meningeal irritation, as shown in cases of tumors of the brain or spinal cord. In our series of fourteen cases of such a condition, each verified by operation or

TABLE 8.—Multiple Sclerosis

| Hospital No. | Nonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|
| 8977 | — | 6 | 1111000000 | — |
| 13010 | — | 1 | — | — |
| 12237 | — | 1 | — | — |
| 10222 | ± | 2 | — | — |
| 12950 | — | 1 | — | — |
| 13005 | — | 1 | — | — |
| 14086 | — | 25 | 1133320000 | — |
| 13091 | + | 8 | 0232100000 | — |
| 13180 | ± | 7 | 0122110000 | — |
| 14517 | — | 3 | 2331000000 | — |
| 14814 | — | 1 | — | — |
| 9048 | ± | 4 | 5433310000 | — |
| 10117 | ± | 10 | 2333200000 | — |
| 10466 | — | 2 | — | — |
| 14821 | — | 2 | — | — |
| 16079 | — | 8 | 1122331100 | — |
| 16422 | — | 2 | 0012100000 | — |
| 16464 | — | 2 | — | — |
| 16775 | + | 0 | 1555552200 | — |

TABLE 9.—Meningitis

| Hospital No. | Nonne | Cells | Colloidal Gold | Wassermann | Type |
|---|---|---|---|---|---|
| 9117 | + | 32 | 1100000000 | + | Tuberculosis |
| 8569 | ++ | 112 | 0000000123 | — | Tuberculosis |
| B. | +++ | 300 | 0114444321 | — | Pneumococcus |
| C. | +++ | 340 | 0000002321 | — | Tuberculosis |
| 16780 | ++ | 281 | 0003555410 | — | Tuberculosis |
| H. | ++ | 250 | 0000124442 | — | Tuberculosis |

TABLE 10.—Tumors of Brain and Cord

| | Nonne | Cells | Colloidal Gold | Cerebrospinal Fluid Wassermann |
|---|---|---|---|---|
| Total cases | 14 | 10 | 14 | 14 |
| + | 6 = 42.85% | 3 = 30% | 8 = 57.1% | 1 = 7.64% |
| ± | 2 = 14.28% | | 1 = 7.1% | |
| — | 6 = 42.85% | 7 = 70% | 5 = 35.7% | 13 = 92.85% |

TABLE 11.—Cord and Brain Tumors

| Hospital No. | Nonne | Cells | Colloidal Gold | Wassermann | Type |
|---|---|---|---|---|---|
| 9833 | — | 1 | — | — | Gliosarcoma |
| 9006 | + | 30 | 0002333210 | — | Gumma |
| 8869 | — | 13 | 0002333100 | — | Gumma |
| 8170 | + | 2 | 0011223334 | — | Sarcoma of spine |
| 11487 | + | 5 | 2222333311 | — | Glioma |
| 12788 | — | — | — | — | Sarcoma of cord |
| 13715 | — | 4 | — | — | Gumma |
| 10886 | + | 12 | 0112333000 | + | Gumma |
| 9720 | ++ | 5 | 0000012222 | — | Sarcoma |
| 13570 | — | — | — | — | Cerebellar sarcoma |
| 16390 | — | 0 | — | — | Brain tumor |
| 16249 | — | 1 | 4444320000 | — | Brain abscess |
| 16669 | ++ | 4 | 0000012555 | — | Cord tumor |
| M. | ++ | 4 | 0000012555 | — | Cord tumor |

necropsy, such a curve was present in eight cases. This is of special value when found in these conditions accompanied by negative or faintly positive Nonne and a low cell count, while meningitis, on the other hand, has its curve accompanied by + + or + + + Nonne and a high cell count.

MISCELLANEOUS CASES

Our series of miscellaneous cases is made up of general medical and surgical cases, neurologic cases not coming under any of the special headings, and cases of syphilis where the central nervous system is not definitely involved. Of this group, twenty-five fluids gave some curve including four very slight reductions — not over "1"; only fifteen were curves that are ordinarily regarded as significant. Eight of these were in cases which presented clinical or laboratory evidence of syphilis, of which three had involvement of the nervous system (sciatica, myelitis and paralysis agitans).

TABLE 12.—MISCELLANEOUS CASES

| | Nonne | Cells | Colloidal Gold | Cerebrospinal Fluid Wassermann |
|---|---|---|---|---|
| Total cases | 243 | 233 | 240 | 239 |
| + | 10 = 4.11% | 1-5 inc. = 230 cases | 7 | 0 |
| ± | 12 = 4.94% | 6 and over = 3 cases | 14 | 0 |
| − | 221 = 90.95% | Aver. = 1.618 | | 239 |

Of the seventeen nonsyphilitic cases giving curves

12 had involvement of the nervous system:

3 = tumor of cord or brain
2 = progressive muscular atrophy
2 = nonsyphilitic myelitis or encephalitis
2 = multiple neuritis (very slight reduction)
1 = essential epilepsy (very slight reduction)
1 = sciatica
1 = Alcoholic psychosis

5 showed no neurologic findings:

1 = acute bronchitis
1 = chronic vulvitis
1 = reserved diagnosis
1 = myxedema
1 = cirrhosis of the liver

Of the three cell counts over 6 one was a case of syphilis with a cell count of 12 and a slight colloidal gold curve; one was a case of psychasthenia and gave a count of 6; and the third was a case of "optic atrophy" with a slight positive Nonne and a cell count of 8.

TABLE 13.—Miscellaneous Cases

| Hosp. No. | Diagnosis | Xonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|---|
| 7894 | Cardiac syphilis | — | 1 | 0001210000 | — |
| 8498 | General syphilis | — | 1 | — | — |
| 9633 | Syphilis of bladder | — | 2 | — | — |
| 10953 | Tertiary syphilis | — | 1 | — | — |
| 10898 | Syphilis of tibia | — | 5 | — | — |
| 10894 | General syphilis | — | 2 | — | — |
| 10323 | General syphilis | ± | 1 | — | — |
| 10984 | General syphilis | — | 2 | — | — |
| 11256 | General syphilis | — | 1 | — | — |
| 11481 | Tuberculosis of larynx and syphilis | — | 12 | 1112210000 | — |
| 11981 | Nephritis and syphilis | + | 1 | 1111221000 | — |
| 12680 | General syphilis | ± | 1 | 1112220000 | — |
| 12601 | General syphilis | — | 1 | 1133321000 | — (Dispensary case) |
| 12996 | Syphilitic iritis | — | 2 | — | — |
| 14324 | General syphilis | — | 1 | — | — |
| 14259 | General syphilis | — | 1 | — | — |
| 14329 | General syphilis | — | 1 | — | — |
| 15060 | General syphilis | — | 1 | — | — |
| 15043 | Syphilitic aortitis | — | 3 | — | — |
| 16108 | Paralysis agitans and syphilis | — | 3 | 0012221000 | — |
| 16236 | Congenital syphilis | — | 1 | — | — |
| 16510 | Aortic aneurism | + | 2 | 0001221000 | — |
| 8890 | Combined sclerosis | — | 1 | — | — |
| 8150 | Pernicious anemia | — | 2 | — | — |
| 9037 | Pernicious anemia | — | 2 | — | — |
| 10882 | Combined sclerosis | + | 2 | — | — |
| 10712 | Combined sclerosis | — | 1 | — | — |
| 13589 | Pernicious anemia | — | 1 | — | — |
| 13808 | Combined sclerosis | — | 1 | — | — |
| 14794 | Combined sclerosis | — | 3 | — | — |
| 15696 | Pernicious anemia | — | 1 | — | — |
| 15803 | Pernicious anemia | — | 1 | — | — |
| 16709 | Combined sclerosis | — | 0 | — | — |
| 9850 | Sciatica and syphilis | ± | 2 | 0122220000 | — |
| 11316 | Sciatica | — | 1 | — | — |
| 12874 | Sciatica | — | 1 | — | — |
| 13102 | Sciatica | — | 1 | — | — |
| 14055 | Sciatica | — | 2 | — | — |
| 14318 | Sciatica | ± | 6 | 1133310000 | — |
| 16345 | Sciatica | — | 1 | — | — |
| 9857 | Epilepsy | — | 1 | — | — |
| 10832 | Epilepsy | — | 2 | — | — |
| 11211 | Epilepsy | — | 1 | — | — |
| 12823 | Epilepsy | — | 1 | — | — |
| 12527 | Epilepsy | — | 1 | 0111000000 | — |
| 13582 | Epilepsy | — | 1 | — | — |
| 14832 | Epilepsy | — | 2 | — | — |
| 14040 | Epilepsy | — | 4 | — | — |
| 14435 | Epilepsy | — | 1 | — | — |
| 14435 | Epilepsy | — | 2 | — | — |
| 14301 | Epilepsy | — | 1 | — | — |
| 16392 | Epilepsy | — | 3 | — | — |
| N. | Epilepsy | — | 1 | — | — |
| 9870 | Paralysis agitans | — | 3 | — | — |
| 11137 | Paralysis agitans | — | 1 | — | — |
| 14449 | Paralysis agitans | — | 3 | — | — |
| 16293 | Paralysis agitans | — | 1 | — | — |
| 8. | Paralysis agitans | ± | 6 | — | — |
| 16796 | Paralysis agitans | — | 1 | — | — |
| 14449 | Paralysis agitans | — | 1 | — | — |
| 9788 | Multiple neuritis | — | 2 | — | — |
| 10793 | Chronic lead poisoning | — | — | 0012210000 | — |
| 10464 | Polyneuritis | — | 2 | 1111100000 | |
| 10657 | Chronic neuritis | — | 3 | — | — |
| 15431 | Postdiphtheritic paralysis | — | 1 | — | — |
| 9279 | Hemiplegia | — | 1 | — | — |
| 11217 | Thrombosis of cerebellum | — | 2 | — | — |
| 13377 | Hemiplegia | — | 1 | — | — |
| 13710 | Old hemiplegia | — | 1 | — | — |
| 13288 | Hemiplegia | — | 1 | — | — |
| 13461 | Right hemiplegia | — | 2 | — | — |
| 16076 | Cerebral hemorrhage | + | 2 | — | — |
| 16176 | Cerebral hemorrhage | — | 2 | — | — |
| 16725 | Cerebral hemorrhage | — | 3 | — | — |

TABLE 13.—MISCELLANEOUS CASES—(*Continued*)

| Hosp. No. | Diagnosis | Nonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|---|
| 9963 | Muscular dystrophy | — | 1 | — | — |
| 10128 | Bulbar palsy | — | 1 | — | — |
| 10272 | Progressive muscular atrophy | — | 1 | 11132100000 | — |
| 12041 | Progressive muscular atrophy | + | — | 1111100000 | — |
| 14641 | Amyotrophic lateral sclerosis | — | 2 | — | — |
| 14586 | Progressive muscular atrophy | — | 2 | — | — |
| 15064 | Progressive muscular atrophy | — | 3 | — | — |
| 14641 | Amyotrophic lateral sclerosis | — | 3 | — | — |
| 9751 | Transverse myelitis | — | 1 | — | — |
| 10740 | Myelitis | + | 1 | 0000022245 | — |
| 14715 | Encephalitis | — | 1 | — | — |
| 16204 | Myelitis, syphilitic | — | 5 | 2223310000 | — |
| 16369 | Myelitis | +++ | 1 | 0124444444 | — |
| 11319 | Traumatic neurosis | — | 1 | — | — |
| 11622 | Neurasthenia | — | 1 | — | — |
| 11410 | Traumatic neurosis | — | 1 | — | — |
| 12270 | Neurasthenia | — | 1 | — | — |
| 13088 | Neurasthenia | — | 1 | — | — |
| 13062 | Neurasthenia | — | 2 | — | — |
| 13650 | Neurasthenia | — | 1 | — | — |
| 13628 | Hysteria | — | 1 | — | — |
| 13679 | Neurasthenia | — | 1 | — | — |
| 13118 | Neurasthenia | — | 1 | — | — |
| 13143 | Neurasthenia | — | 1 | — | — |
| 13481 | Hysteria | — | 3 | — | — |
| 13807 | Hysteria | — | 1 | — | — |
| 14020 | Neurasthenia | — | 1 | — | — |
| 14487 | Neurasthenia | — | 1 | — | — |
| 14588 | Hysteria | — | 1 | — | — |
| 14384 | Neurasthenia | — | 1 | — | — |
| 14186 | Neurasthenia | — | — | — | — |
| 14285 | Neurasthenia | — | 1 | — | — |
| 14558 | Hysteria | — | 2 | — | — |
| 14402 | Neurasthenia | — | 0 | — | — |
| 14680 | Psychasthenia | — | 1 | — | — |
| 15629 | Neurasthenia | — | 1 | — | — |
| 15021 | Neurasthenia | — | 2 | — | — |
| 16094 | Neurasthenia | — | 1 | — | — |
| 16149 | Neurasthenia | — | 1 | — | — |
| 16428 | Hysteria | — | 1 | — | — |
| 14384 | Psychasthenia | — | 6 | — | — |
| 10965 | Dementia praecox | — | 1 | — | — |
| 14565 | Dementia praecox | — | 1 | — | — |
| 14447 | Senility | — | 2 | — | — |
| 14522 | Dementia | — | 1 | — | — |
| 16111 | Senility | — | 1 | — | — |
| K. | Melancholia | + | 1 | — | — |
| 16759 | Cyclothymia | — | 1 | — | — |
| G. | Alcoholic psychosis | — | 0 | 0013110000 | — |
| 8743 | Senile paraplegia | — | 4 | — | — |
| 9236 | Optic neuritis | — | 1 | — | — |
| 10965 | Chronic progressive chorea | — | 1 | — | — |
| 10591 | Pachymeningitis | — | 1 | — | — |
| 11299 | Syringomyelia | — | 1 | — | — |
| 12985 | Fracture of skull | — | 1 | — | — |
| 13000 | Myasthenia gravis | — | 1 | — | — |
| 12661 | Hydrocephalus | — | 1 | — | — |
| 13729 | Cervical rib | — | 1 | — | — |
| 13775 | Cervical rib | — | 1 | — | — |
| 12959 | Fracture of spine | — | 1 | — | — |
| 14591 | Cerebellar atrophy | — | 2 | — | — |
| 14590 | Lateral sclerosis | — | 2 | — | — |
| 15896 | Caries of vertebrae | — | 2 | — | — |
| D. | Optic atrophy | ± | 8 | — | |
| 16440 | Chorea | — | 1 | — | — |
| 12408 | Myxodema | — | 3 | 0121000000 | — |
| 14231 | Hyperthyroidism | — | 1 | — | — |
| 15812 | Adenoma of thyroid | — | 2 | — | — |
| 15092 | Exophthalmic goiter | — | 2 | — | — |
| 16758 | Hyperthyroidism | — | 2 | — | — |
| 10931 | Obesity | — | 2 | — | — |
| 16994 | Obesity | — | 0 | — | — |
| 11914 | Diabetes mellitus | — | 1 | — | — |
| 14475 | Diabetes mellitus | — | 3 | — | — |
| 16194 | Diabetes mellitus | — | 1 | — | — |
| 14475 | Diabetes mellitus | — | 1 | — | — |

TABLE 13.—Miscellaneous Cases—(*Continued*)

| Hosp. No. | Diagnosis | Nonne | Cells | Colloidal Gold | Wassermann |
|---|---|---|---|---|---|
| 8845 | Chronic valvular disease | — | 1 | — | — |
| 9949 | Mitral stenosis | — | 2 | — | — |
| 10580 | Aneurism of aorta | — | — | — | — |
| 12238 | Angina pectoris | — | 1 | — | — |
| 12476 | Arteriosclerosis | — | 3 | — | — |
| 13802 | Arteriosclerosis | — | 5 | — | — |
| 13987 | Chronic endocarditis | — | 1 | — | — |
| 13555 | Chronic myocarditis | — | 1 | — | — |
| 14206 | Valvular disease | — | 1 | — | — |
| 14234 | Cardiac | — | 1 | — | — |
| 15084 | Mitral stenosis | — | 2 | — | — |
| 16205 | Arteriosclerosis | — | 1 | — | — |
| 15840 | Lymphatic leukemia | — | 1 | — | — |
| 16357 | Acute pericarditis | — | 0 | — | — |
| 16880 | Cardiac disease | — | 2 | — | — |
| 16216 | Arterial calculus | — | 0 | — | — |
| 10700 | Arteriosclerosis | — | 1 | — | — |
| 10912 | Bronchitis | — | 1 | — | — |
| 10494 | Pulmonary tuberculosis | — | 2 | — | — |
| 10551 | Acute bronchitis | — | 1 | 0022100000 | — |
| 10639 | Pulmonary tuberculosis | — | 1 | — | — |
| 14332 | Pulmonary tuberculosis | — | 1 | — | — |
| 15033 | Miliary tuberculosis | — | 3 | — | — |
| 15970 | Asthma | — | 4 | — | — |
| 15704 | Pulmonary tuberculosis | — | 1 | — | — |
| 16464 | Chronic pulmonary lesion | — | 2 | — | — |
| 16346 | Pneumonia | — | 4 | — | — |
| 16880 | Acute miliary tuberculosis | — | 1 | — | — |
| 10879 | Arthritis | — | 1 | — | — |
| 11727 | Multiple arthritis | — | 1 | — | — |
| 14251 | Chronic arthritis | — | 3 | — | — |
| 13044 | Arthritis | — | 2 | — | — |
| 16784 | Chronic polyarthritis | — | 1 | — | — |
| 10956 | Gastric carcinoma | — | 1 | — | — |
| 12407 | Carcinoma of prostate | — | 1 | — | — |
| 16808 | Diffuse carcinomatosis | — | 2 | — | — |
| 9957 | Gastric carcinoma | — | 1 | — | — |
| 9985 | Refractive error | — | 1 | — | — |
| 10357 | Refractive error | — | 1 | — | — |
| 12733 | Reserved | — | 2 | — | — |
| 12470 | Reserved | — | 1 | 0011100000 | — |
| 12489 | Reserved | — | 1 | — | — |
| 10280 | Gingivitis | — | 1 | — | — |
| 16535 | Gingivitis | — | 2 | — | — |
| 13054 | Duodenal ulcer | — | 2 | — | — |
| 16552 | Duodenal ulcer | — | 2 | — | — |
| 16073 | Duodenal ulcer | — | 1 | — | — |
| 13551 | Cystitis | — | 1 | — | — |
| 14406 | Chronic cystitis | — | 1 | — | — |
| 14409 | Chronic cystitis | — | 2 | — | — |
| 14483 | Appendicitis | — | 1 | — | — |
| 14482 | Appendicitis | — | 2 | — | — |
| 14114 | Chronic amygdalitis | — | 2 | — | — |
| 16763 | Amygdalitis | — | 1 | — | — |
| 14487 | General debility | — | 2 | — | — |
| 8. | General debility | — | 3 | — | — |
| 9959 | Hereditary contraction of finger | — | 2 | — | — |
| 10808 | Atrophy of testicle | — | 2 | — | — |
| 10720 | Pregnancy | — | — | — | — |
| 10180 | Chronic gastritis | — | 1 | — | — |
| 11077 | Adhesions of cecum | — | 1 | — | — |
| 11173 | Prolapsed urethra | — | 1 | — | — |
| 12213 | Pyelitis | — | 1 | — | — |
| 12639 | Chronic vulcitis | — | 1 | 0012210000 | — |
| 10786 | Ulcer of foot | — | 1 | — | — |
| 12128 | Inguinal hernia | — | 1 | — | — |
| 12908 | Chronic nephritis | — | 1 | — | — |
| 13392 | Fracture | — | 1 | — | — |
| 13324 | Periostitis of os calcis | — | 1 | — | — |
| 14021 | Pyelonephrosis | — | 1 | — | — |
| 14413 | Visceroptosis | — | 2 | — | — |
| 14781 | Infectious diarrhea | — | 1 | — | — |
| 16257 | Nephrolithiasis | — | 4 | — | — |
| 16904 | Cholecystitis | — | 1 | — | — |
| 16453 | Gastric ulcer | — | 4 | — | — |

It is not at all improbable that the six syphilitic cases, coming, as they did, to our attention because of the positive blood Wassermann only, and giving no definite clinical evidence of involvement of the nervous system, will eventually develop clear cut signs of neurosyphilis. Of the thirteen definitely positive curves, twelve occurred in cases either of general syphilis or disease of the nervous system.

This series shows quite conclusively that even a very slight precipitation of the colloidal gold is suggestive of involvement of the nervous system and a reduction of any magnitude is a definite indication of such a condition, and also that a negative curve, especially when unaccompanied by clinical symptoms, is definite ground for ruling out organic lesions of the central nervous system. Although our series of cases of epilepsy is too small to justify any conclusions concerning the colloidal reaction in this disease, it is of interest to note that not one curve was found. While, on the other hand, Larkin and Cornwall[46] in 114 colloidal gold tests done on epileptic patients obtained no curve in 46 per cent., a low curve to "2" in 46 per cent., and a higher curve to "3" in 8 per cent.

### VALUE OF COLLOIDAL GOLD TEST IN TREATED CASES

In reviewing the literature one is impressed with the great variance of opinion on the value of the colloidal gold test in treated cases. Lange in his first presentation of the test claimed that it closely paralleled the clinical course. Eskuchen noted a general paresis curve change to a syphilitic curve. Solomon and Koefod found no marked change of the curve in treated cases, and concluded that there was no relation between the curve and the duration and severity of the disease. Swalm and Mann stated that in remissions and treatment a paretic curve may be lost or changed to one of a syphilitic type. Black, Rosenberg and McBride thought that the colloidal gold test was the last reaction to become negative under treatment, and also saw it change in type during the process. Mehrtens[47] found the reaction steadily decreasing and becoming atypical under treatment. De Crinis and Frank found that as a patient improves the colloidal gold curve returns to normal. Farnell[48] noted that paretic curves under prolonged mercurial or arsenical treatment decreased in intensity, but a few remained unchanged even under prolonged intraspinous treatment. Hammes found that a change in the curve during treatment rarely

46. Larkin and Cornwall: Spinal Fluid in Epilepsy, J. Lab. & Clin. M. **4**:352, 1919. Larkin: Laboratory Diagnosis in Neurosyphilis, Am. J. Syphilis **3**:76, 1919.

47. Mehrtens: Discussion, California State M. J. **16**:170, 1918.

48. Farnell: Observations on the Colloidal Gold Reaction, Providence M. J. **16**:158, 1915.

occurred. Miller and Levy considered that the reaction remained unchanged, both in remissions and under intensive intraspinous treatment; in their series only one case showed a curve diminishing with clinical improvement. Ayer[49] observed that all spinal fluid tests are of little value in indicating progress under treatment. Grulee and Moody reported one case of congenital syphilis which gave a positive colloidal gold reaction at six weeks of age, which, under treatment, became negative at thirteen weeks, and therefore they concluded that treatment modifies the reaction but to a less degree than the Wassermann. Kaplan and McClelland found that the paretic curve resists all treatment and consider the condition analogous to that known as "Wassermann fast." Solomon and Southard noted that any one test may remain positive after all the other tests become negative; therefore, concluded that the laboratory reactions never parallel the clinical findings. Cornwall[50] notes that a curve may be temporarily increased after treatment.

Our series of treated cases is too small and the results are too variable to permit of any conclusions. The following observations, however, may be of some interest.

Our usual method of treatment in the hospital consists of weekly intravenous injections of arsphenamin (occasionally neoarsphenamin) followed by spinal drainage twenty minutes later; this treatment is preceded by a few doses of mercury and iodids, which treatment was sometimes continued during the intravenous treatment, the arsphenamin being alternated with the mercury. A few of the earlier cases were given arsphenaminized serum intraspinously. It is noteworthy that with this method of therapy the fluid not infrequently gave more marked reactions after the second or third treatment, or became positive where negative on the first examination. In later examinations the fluids tended to be less "positive." In a few of our cases all the spinal tests gradually returned to normal under intensive treatment, but even in these the reactions showed no uniformity in the order of their decrease or disappearance.

Many of the fluids, however, gave little or no indication of change of reaction while, at the same time, the patient gave marked clinical evidence subjectively and objectively of betterment. Therefore, one is justified in the assumption that the colloidal gold curve, while of very definite value in initial diagnosis, is often practically useless in treated cases, either for diagnosis or prognosis, and has been found not to

49. Ayer: Rational Use of Spinal Puncture, J. Nerv. & Ment. Dis. **46**: 429, 1917.

50. Cornwall: Syphilis in Its Relation to the Central Nervous System, Mil. Surgeon **43**:510, 1918.

parallel clinical symptoms. This is well illustrated by several of our cases in which at times during courses of treatment negative curves were obtained and in which later typical reactions resulted.

In our experience, fluids showing pronounced curves did not change to any marked degree during treatment; while provocative or slight reactions often gave temporarily or permanently negative findings.

We had opportunity of examining the fluids of several patients at intervals covering months or a year and more, and it was interesting to note the constancy of the colloidal gold curve. One patient who was receiving intensive treatment gave practically the same curve for three years.

## GENERAL DISCUSSION

The foundation for the colloidal gold reaction was laid by Zsigmondy,[51] who found that "certain colloids, especially proteins," had a protective action on the precipitation of colloidal gold suspensions by sodium chlorid — an electrolyte. The protective value of each protein examined varied, different amounts of each protein being necessary to protect 5 c.c. of colloidal gold against 0.5 c.c. of a 10 per cent. solution of sodium chlorid. It was Lange, however, who applied this test to the quantitative study of the protein in the cerebrospinal fluid. Lange considered it as an indication of the mixture of the protein, but Weston has shown that the substance is dialyzable through thimbles impermeable to albumins and can be precipitated by ammonium sulphate and is, therefore, a globulin.

Zaloziecki[52] thought it was an immunity reaction. Jaeger and Goldstein regarded it as a physical phenomenon, probably of an electrical nature. Eskuchen looked on the cause of the precipitation as due to the pathologic increase of the albumin; variations in the type of precipitation are apparently caused by various forms of physicochemical relations of the albumin.

Solomon and Koefod experimented on adding arsphenamin to the gold solutions; they obtained definite color reactions, but found that normal spinal fluids in varying dilutions up to 1:5,120 protected the solution against this color change. Felton said the zonal reactions are caused by the interrelationship of the globulin and albumin; the albumin protects and the globulin precipitates the gold.

In considering the comparative worth of the various tests used in the clinical study of cerebrospinal fluid it must be borne in mind that each test depends on a different substance in the cerebrospinal fluid

51. Zsigmondy: Die hochrothe goldlösung als reagens auf colloide, Fresemius Ztschr. f. analytische Chem. **40**:697, 1901.

52. Zaloziecki: Ueber den Eiweissgehalt der Zerebrospinalflüssigkeit, Ztschr. f. Nervenh. **47**:783, 1913.

and is indicative of a more or less specific reaction on the part of certain tissues of the nervous system or of a decreased or altered permeability of the choroid plexus. While commonly a rather constant relationship exists between the various reactions in certain types of lesions of the nervous system yet it is amply demonstrated that any one of the reactions may be present when the others are absent, and that the type or degree of the reaction may vary widely from that of any other reaction. To illustrate: in tabes dorsalis a typical laboratory report may read: Nonne +; cells 40; colloidal gold 133 4432000; Wassermann +. But it is evident that the same substance is not responsible for all these findings, for any one or more of these tests may be positive and the others be negative.

Furthermore, none of these tests depends on a common provoking substance, for many conditions will cause increased albumin and globulin in the cerebrospinal fluid; the same is true of the varying degree of cellular increase; the colloidal gold curve and the complement fixation tests are more specific, but even here we find the colloidal gold curves of dementia paralytica and cerebrospinal syphilis occurring in cases of multiple sclerosis and brain abscess.

From the fact that these reactions can occur in diseases of different etiology, it is apparent that the reactions are dependent on various types of tissue change rather than on modified forms of the *Treponema pallidum*, as we might suppose if these reactions occurred only in syphilitic lesions of the central nervous system. It is possible, however, that various forms or fractions of the organism may tend to involve certain tissues more than others.

It is evident that a definite diagnosis should not be made on the presence of one of these reactions other than that any distinct abnormality of the cerebrospinal fluid indicates a pathologic condition of the central nervous system. One can understand that it would be possible to have a positive Wassermann reaction in the spinal fluid without definite syphilis of the nervous system, due, perhaps, to an altered permeability of the choroid plexus or to a high concentration of antibodies in the blood.

As Felton and Maxy have pointed out, "zonal" reactions are not specific and should not be designated by descriptive terms.

While emphasizing the nonspecificity of the color changes in the various dilutions it is our experience that they are of diagnostic value if corroborated by, or corroborative of, any other reactions or clinical findings. Thus, a reaction in zone I usually means dementia paralytica, in zone II, cerebrospinal syphilis or tabes dorsalis, and in zone III, meningitis.

We had two interesting illustrations of this recently. A patient who had tabo-paresis, with clinical evidence of pachymeningitis hypertrophica cervicalis, gave definite color changes into zones II and III. The second patient was admitted to the hospital in a state of delirium with no history except that he had been sick a week or more. Well marked signs of meningitis were present and examination of the chest suggested the presence of pulmonary tuberculosis. The spinal fluid was under increased pressure and was perfectly clear. A diagnosis of tuberculous meningitis was made. No bacteria were found in the fluid on repeated examinations and the colloidal gold solution was almost completely reduced in all except the first dilution. This suggested a cerebrospinal syphilis in addition to the meningitis. This was confirmed by repeated positive blood and spinal fluid Wassermanns. Under antisyphilitic treatment the patient improved markedly and the meningitic symptoms cleared up largely.

Textbooks and observers frequently differ as to the cell count to be considered as pathologic, the most common view, however, being that any number below 10 is normal. Many writers feel that this is too high a limit. Kafka considers anything above 5 as pathologic. Dreyfus[53] gives the following classification: 1 to 5, normal; 6 to 9, doubtful; 10 to 20, slight pleocytosis; 21 to 50, moderate pleocytosis, and over 50 as a marked pleocytosis. Black and Vernes[54] believed that the count considered normal was too high, and from their own observations concluded that less than one lymphocyte was a normal count and that two or three lymphocytes should be considered as pathologic. Genoese[55] considers more than one lymphocyte distinctly pathologic.

In our series there was not a single count of over five cells in a nonsyphilitic or non-neurologic case, and the average was 1.6 cells in our normal spinal fluids. From this fact as well as the findings of others we believe that five should be the limit of a normal cell count.

The consensus of opinion seems to be that we have practically always a pleocytosis in syphilis of the central nervous system, but Mitchel, Darling and Newcomb,[56] making 300 counts on 34 patients, with untreated syphilis, in two weeks, found great variations in short intervals in every stage of the disease; either high or low counts appearing at any time in the disease, persisting for months, or chang-

53. Dreyfus: Die Methoden der Untersuchung des Liquor cerebrospinalis bei Syphilis, München. med. Wchnschr. **59**:2561, 1912.

54. Black and Vernes: Les lymphocytes du liquide Cephalorachidiens normal, Compt. rend. Soc. de biol. **75**:231, 1918.

55. Genoese: The Cerebrospinal Fluid During Malaria in Children, Policlinico **26**:737, 1919.

56. Mitchel, Darling and Newcomb: Observations on Spinal Fluid Cell Count in Untreated Cases of Cerebrospinal Syphilis, J. Nerv. & Ment. Dis. **41**:686, 1914.

ing completely in intervals of only a few weeks. They also failed to find any parallelism between changes in the cell count and clinical symptoms.

Solomon and Koefod in a study of spinal fluid cellular content in cases of syphilis of the central nervous system after treatment found that the number of cells may vary greatly, changing from normal to high counts or from high to low counts within a few days. They conclude that the number of cells gives no definite information on duration, severity, or prognosis of the disease and is of no value in differentiating between cerebrospinal syphilis and dementia paralytica.

Lowrey in a study of what he terms "brain lues" reports the following results: 3 or 4 cells in four cases; from 5 to 10 cells in thirteen cases; from 11 to 25 cells in twenty cases; from 26 to 50 cells in twenty-six cases; from 51 to 100 cells in thirty-eight cases, and from 101 to 250 cells in twenty-seven cases, showing that an appreciable number of patients had low counts.

From a study of the repeated fluid examinations in treated and untreated cases we find a somewhat greater reduction of the number of cells in long treated than in untreated cases. There was, however, great variability in the counts at different times and the findings in general agree with those mentioned above.

The colloidal gold reaction, while requiring a careful technic, has been simplified by careful workers until it is easily within the reach of any routine laboratory. It is also unquestionably the most sensitive and valuable of the various tests used in a study of the spinal fluid. It does not usurp the place of any of the other tests nor make a careful neurologic examination unnecessary, but does have a definite and independent value, and no examination of the spinal fluid is complete without it.

As Fildes, Parnell and Maitland,[57] and Wile and Stokes[58] have pointed out, the spinal fluid may give evidence of involvement of the central nervous system early in the course of syphilitic infection. Since early treatment is of such vital importance in neurosyphilis, it is essential that in every case of general syphilis, especially with any signs of nervous system involvement, a complete study of the spinal fluid should be made as well as a careful neurologic examination.

On contemplating the large amount of literature on the subject one is impressed by the fact that the colloidal gold reaction has passed through the stage of experimentation with resulting over-expectation

57. Fildes, Parnell and Maitland: Unsuspected Involvement of the Central Nervous System, Arch. Neurol & Psychiat. **1**:231 (Feb.) 1919.

58. Wile and Stokes: Involvement of the Nervous System During the Primary Stage of Syphilis, J. A. M. A. **64**:979 (March 20) 1915.

and exploitation, then the reactionary period of comparative neglect and indifference, and now has reached the intermediate and permanent stage of acceptance, occupying an independent position of its own and forming a necessary part of every routine laboratory spinal fluid analysis and careful neurologic examination. With Lange we believe that this reaction often determines the presence of an early and slight involvement of the nervous system and is, therefore, of great importance in early diagnosis, permitting of early treatment and thereby preventing or modifying severe syphilitic and "metasyphilitic" diseases of the central nervous system.

SUMMARY

1. The colloidal gold test is the most delicate of the routine spinal fluid reactions.

2. With careful technic and proper attention to neutrality successful colloidal gold solutions are within the reach of every laboratory worker.

3. It does not replace any other test but, on the other hand, is of independent value.

4. It is of especial importance in the early diagnosis of neurosyphilis.

5. The various curves are not specific but are of great diagnostic value in conjunction with other clinical and laboratory findings.

6. A colloidal gold curve may be obtained with or without other positive findings after provocative treatment.

7. The colloidal gold curve does not parallel clinical signs nor give definite evidence of improvement under treatment.

8. Patients with no involvement of the central nervous system or who are nonsyphilitic give no colloidal gold curve.

9. Clear-cut clinical cases of tabes dorsalis may show all the spinal fluid reactions negative both before and after treatment.

10. A curve in zone III with a negative cell count and negative or faintly positive globulin is strongly suggestive of a brain or cord tumor or myelitis.

11. Curves in zones I and II may be found in nonsyphilitic conditions, such as multiple sclerosis and brain abscess.

12. A cell count above five is pathologic, but the cell count is of no value in indicating duration or severity of the process or improvement.

13. This reaction should be included in every spinal fluid analysis and neurologic examination as well as in all cases of general syphilis.

# AN ANALYSIS OF THE SPREAD OF THE EXCITATION WAVE IN THE HUMAN VENTRICLE

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We are now in the possession of a method and sufficient anatomic and physiologic information for a detailed and fairly accurate analysis of the normal and pathologic spread of the excitation wave in the human heart. Such an analysis will help to clarify some of our somewhat hazy and even inaccurate ideas as to the causes of the form of the normal and pathologic electrocardiogram. Using the method of the equilateral triangle devised by Einthoven,[1] I attempted an analysis of the propagation of the wave of electronegativity in the human heart in 1914.[2] This paper has for its purpose the more extended introduction of the method among American clinicians and a revision of some of the ideas developed in that paper. The work of Rothschild and Lewis[3] on the velocity of conduction in the heart muscle has been especially helpful in revising our ideas as to the propagation of the electronegative wave in the heart.

Let us first consider the propagation of the wave of electronegativity in a straight muscle cylinder (Fig. 1, *A-B*) immersed in a physiologic salt solution contained in a glass cylinder (Fig. 1, *C-D*). The two ends of this glass cylinder are connected by nonpolarizable electrodes with a string galvanometer. If the muscle is stimulated at *X* this point becomes electronegative with respect to the rest of the muscle mass, currents of electricity flow in the tissue juices surrounding the muscle fibers and in the physiologic salt solution in which it is immersed. There is a difference of potential between the ends *C* and *D* of the glass cylinder. Just as the end *B* of the muscle cylinder is more negative than the end *A*, so also the end *D* of the glass cylinder is more negative than the end *C*, and a current of positive electricity will run in the galvanometer from *C* to *D*; conversely, the direction of the galvanometer deflection will indicate to the observer which end of the muscle has been thrown into the state of excitation. From *x* the excitation process will spread toward both ends with equal velocity. The end *B* will receive the electronegative wave first. At this moment the galvanometer will show the maximum deflection in the original direction. The wave of electronegativity continues its journey toward

1. Einthoven: Fahr u. de Waart: Arch. f. d. ges. Physiol. **150**:275, 1913.
2. Fahr and Weber: Deutsch. Arch. f. klin. Med. **117**:361, 1915.
3. Lewis and Rothschild: Phil. Trans., B, **206**:181, 1915.

*A*, while the electronegativity is dying out at *B*. Finally, the excitation process reaches the end *A;* this point now has its maximum negativity, whereas the point *B* has lost its negativity or is losing it in the normal process of return to the original state. At this moment the point *C* of the glass cylinder is more negative than the point *D*, an electric current runs from *D* to *C* through the galvanometer which shows a deflection in the opposite direction corresponding to the reversal of the direction of the potential difference in the muscle cylinder *A-B* and the glass cylinder *C-D*.

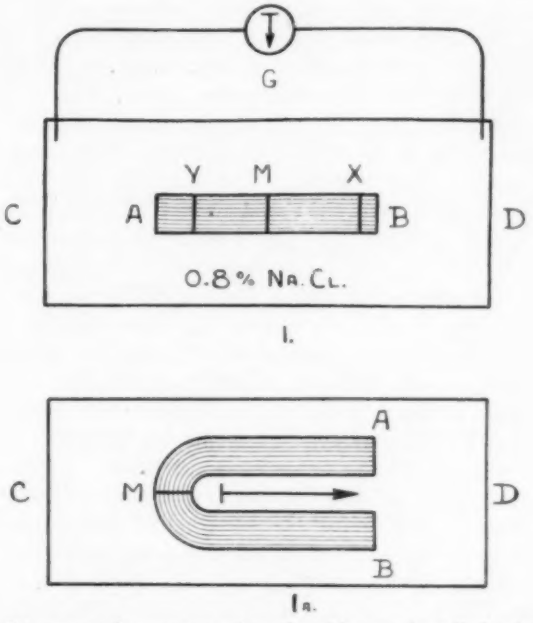



Fig. 1.—Diagrammatic representation of a thin muscle cylinder immersed in physiologic salt solution contained in a very large cylindrical glass vessel with one galvanometer lead.

We have traced the development of a diphasic current in a muscle cylinder stimulated near one end *B* with its spread throughout the muscle mass and have followed the curve described by the string galvanometer in this simple case. If we stimulate the muscle at *y*, the end *A* of the muscle will be more negative than the end *B*, the end *C* more negative than the end *D*, and the current will run from *D* to *C* through the galvanometer indicating to the observer that the muscle is in a state of excitation at a point nearer to its *A* end than its *B* end.

It is necessary to consider the case when the muscle cylinder is stimulated at its center *m*. In this case the electronegative process starts at *m* and travels with equal velocity toward both ends. The ends *A* and *B* will have synchronously the same electrical potentials as the excitation process approaches them. There will be no difference of potential between *A* and *B*, and correspondingly no difference of potential between *C* and *D*. The galvanometer will in this case give no indication of activity in the muscle cylinder. The observer at the galvanometer will receive no indication that an excitation process has started at *m* and spread to both ends.

In the same way if both ends *A* and *B* are thrown into a state of excitation at the same moment, and in consequence both ends become electronegative in respect to points on the muscle near them, then *A* and *B* have equal potentials; in consequence, there will be no difference of potential between *C* and *D*, and the galvanometer will not indicate that there is activity in the muscle, despite the fact that both ends of the muscle mass are in excitation.

There is one more elementary case to be considered. The muscle cylinder is bent at *m* so that the ends *A* and *B* are next to one another, and this V-shaped muscle mass is immersed in the cylinder *C-D* in such a way that the ends *B* and *A* are toward *D*, and the middle *m* lies toward *C* (Fig. 1, *A*). If the muscle is now stimulated at *m*, its middle point, we get a potential difference between *m* and *A*, and between *m* and *B* such that both *A* and *B* are positive to *m*. If we make use of an arrow to indicate the direction of a potential difference, the head indicating positivity and the tail negativity, the arrow in this case will point from *C* toward *D*. *D* is more positive than *C*, and a current passes through the galvanometer from *D* to *C*. The observer noting the direction of the deflection of the galvanometer can thereby determine that the portion of the muscle mass toward *C* is negative in respect to that portion toward *D*. In other words, he can deduce that a portion of muscle more toward *m* than toward *A* and *B* has been thrown into activity. By following the curve of the deflection of the galvanometer he can follow the spread of the activity from *m* toward *A* and *B*, and determine very closely the moment when *A* and *B* are thrown into activity, for at this moment the direction of the galvanometer deflection is opposite and reaches its maximum. Vice versa, if both points *A* and *B* are stimulated and the excitation process spreads toward *m*, the curve of the galvanometer deflection is exactly the reverse of the preceding curve. If *A* alone is first stimulated we have a potential difference such that the end D is negative to the end *C*. As the wave of electronegativity proceeds toward *m* the direction of the potential difference changes. When *m* is negative the ends *A*

and $B$ are positive and the arrow points toward $D$. As the excitation wave spreads further along the muscle it finally approaches $B$, and when it arrives here $B$ is negative to $m$ and $D$ is negative to $C$, and the direction of the potential difference in the salt solution is again changed; that is, the arrow points toward C.

It is possible to twist our schematic muscle cylinder into innumerable shapes and to consider each of these cases as we have considered the above few in detail. But the moment we begin to twist the muscle cylinder into various shapes the electronegative wave travels at certain points in directions at right angles to the direction $C$—$D$. We shall, therefore, next consider a few simple cases of propagation of the excitation process in a muscle mass immersed in a flat rectangular receptacle containing physiologic sodium chlorid solution (Fig. 2).

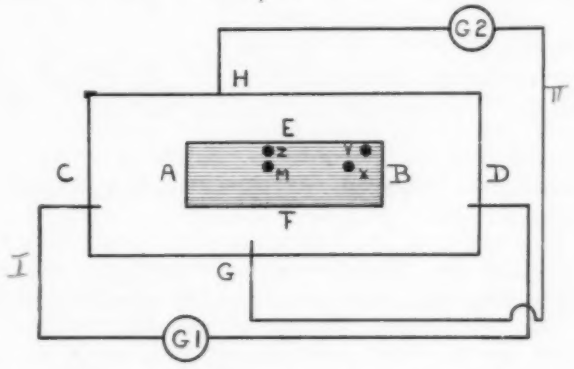


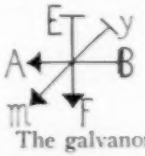
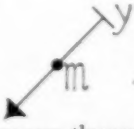

Fig. 2.—Diagrammatic representation of a flat muscle sheet immersed in a flat rectangular vessel of salt solution with two galvanometer leads.

$A$-$B$-$E$-$F$ is the muscle mass. $C$-$D$-$H$-$G$ is the glass vessel filled with the physiologic sodium chlorid solution. One galvanometer ($G1$) is connected to the ends $C$ and $D$, this we shall call lead $I$. The other galvanometer is connected to the sides $H$ and $G$. We shall call this lead II. If the muscle is excited at $x$, the electronegativity is first present at $x$, the rest of the muscle is positive to $x$. The end $B$ is less positive than the end $A$, therefore, as far as these ends are concerned there is a potential difference in the muscle of such direction that an arrow indicating the direction of potential in the muscle fiber will have the direction $A \leftarrow B$ if the head indicates positivity and the tail negativity.

As $x$ is symmetrically placed with respect to the sides $E$ and $F$ there will be no difference of potential between them, and, therefore, no potential difference between $H$ and $G$ and the galvanometer 2 will

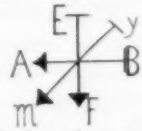
indicate no activity. The galvanometer 1 will be deflected in a direction indicating a potential difference between $C$ and $D$ in such a direction that the current runs from $C$ to $D$. The observer of the galvanometers will see a deflection in lead I and none in lead II, and will conclude that there is a point of activity in the muscle located symmetrically to $E$ and $F$ and nearer $B$ than $A$. He can follow the spread of the excitation process throughout the muscle.

If we stimulate the muscle at $z$ we get no difference of potential between $A$ and $B$ because they are equidistant and symmetrically placed with respect to $z$. There will be a potential difference between $E$ and $F$ of directions $\downarrow_{F}^{E}$ because $z$ is nearer $E$. Galvanometer 1 will show no deflection. Galvanometer 2 will be deflected in a direction indicating current passing from $G$ to $H$, and the observer will conclude from the galvanometer deflections that the muscle is active at a point nearer $E$ than $F$, and equidistant from $A$ and $B$.

If the muscle is stimulated to activity at $y$, $B$ is negative to $A$ because $y$ is nearer $B$, and $E$ is negative to $F$, for $y$ is nearer the side $E$ than the side $F$. There will be a potential difference in the muscle whose direction $ym$  can be resolved into the two components $EF$ and $AB$. The galvanometers are deflected in such a way that lead I indicates $E$ negative to $F$ and lead II indicates $B$ negative to $A$. The observer must combine the two potential differences at right angles to one another in order to get the resultant potential difference. This resultant will indicate to him the point at which the muscle is in activity. For if he gets his resultant and draws it into a figure shaped like  the muscle, drawing it in such a way that the arrow passes through the center of gravity $m$, the negative end $y$ will point toward that area of muscle which is in a state of activity.

If $m$, the center of gravity, is excited, this point is negative with respect to all others, but as the distribution of potential is symmetrical, and as $A$ and $B$ are equidistant and $E$ and $F$ are equidistant from $m$, there will be no potential difference between $E$ and $F$ or between $A$ and $B$. There is no resultant potential difference in the whole mass. It must be remembered that there is a potential difference between $A$ and $m$, but as this is equal and opposite to the potential difference

between $B$ and $m$ they neutralize one another as far as the ends $C$ and $D$ are concerned. And although there is a potential difference $\uparrow_{m}^{E} mE$ and also one $\downarrow_{F}^{m} mF$ these two neutralize one another. There is no potential difference $EF$. Neither galvanometer is deflected. The observer cannot know whether the muscle is inactive or whether there is activity at its center of gravity.

If both $z$ and $x$ are active at the same moment we get two potential differences 

$EF$ and $BA$ which combine to a resultant $ym$. Both galvanometers 1 and 2 are deflected. One indicates negativity at $E$ the other at $B$. The observer can not tell whether he has a resultant potential difference due to stimulation at two points $z$ and $x$, or a potential difference due to stimulation only at a point near $y$. It is true that the potential difference due to stimulation at the two points $z$ and $x$ is of greater magnitude than that due to stimulation at one point, $y$, only. This might help him decide as to the exact point of origin of the stimulus, but it is very easy for the reader to see that as soon as we have to do with the origin and spread of electronegativity in a muscle mass extending in two dimensions of space, with two galvanometer leads, it becomes impossible to determine more than the general direction of a resultant potential difference and its magnitude. We must call in other data to aid us in finding the point of origin and in following the spread of the excitation process. In the heart, for example, many points are stimulated nearly simultaneously and the spread is very rapid. It is only by following the change in direction and magnitude of the resultant potential difference, combined with our knowledge of the architecture of the specific conducting system, that we can analyze the path of the spread in the human ventricle.

The above consideration of certain elementary cases is sufficient to show the reader that the problem of determining the points of a muscle which are in a state of excitation from galvanometer leads applied to points external to the muscle is not an easy one and that we cannot always determine each individual point. We can determine a resultant potential difference by geometrical construction, following the method of combining vectors. If the arrow representing the direction and magnitude of this resultant vector is drawn through the center of gravity of the geometrical figure representing the object, its tail will point in the direction of the center of electronegative mass.

We desire to impress the reader with the fact that it is impossible to determine anything other than the magnitude and direction of this resultant vector of potential difference from the deflections of the

galvanometers both in these simple cases and in the more complicated case of the distribution of electronegativity in the human heart immersed in the conducting substances of the human body.

We have been considering potential differences in one or two dimensional muscles up to the present. The heart is an object of three dimensions. The three leads of electrocardiography lie in the frontal plane and therefore they only indicate potential differences in this plane or the projection upon this plane of potential differences lying in other planes of space. In other words, the electrocardiogram is a frontal projection of electrical distribution in the heart just as the percussion figure, the orthodiagram or the roentgenogram of the heart is a frontal projection of the mass distribution in the heart. These projections appear sufficient at present for practical purposes.

The ventricle is a complicated system of twisted muscle fibers immersed in a conducting medium less simple than our cylinder of physiologic sodium chlorid solution. Moreover, the excitation process in the heart does not start at one point and spread by muscle conduction, but the excitation process starts nearly simultaneously at various points on the endocardial surface, spreading from here outward by muscle conduction.[4] And finally the electrocardiogram is recorded from leads I, II and III; or from right arm and left arm, right arm and left leg and left arm and left leg. We shall, therefore, find it necessary to adopt a schematization of the human body as an electric conductor, and to make use of our knowledge of the architecture of the His-Tawara system and its terminal arborizations in order to follow approximately the spread of the excitation process in the heart.

Einthoven[1] has given us a schema by means of which it is possible to determine the exact direction of the potential difference in the human heart from three synchronous leads at any time in a given heart cycle. I have modified the method slightly so that it is possible to determine graphically from any two leads the exact direction of the potential difference in the heart at any desired moment. By following the changes in direction and magnitude of the vector representing the potential difference in the heart, it is possible to follow the spread of electronegativity throughout the heart.

Einthoven was aided in his search for a simple geometric form on which to base a schema of the distribution of potential in the human body by the fact that the potential differences between the right leg and the left leg are of negligible magnitude in electrocardiography so that the two legs may be regarded as one isoelectric point.[5] He assumed that the distribution of potential on the surface of the body

4. Lewis and Rothschild: Phil. Trans., B **206**:181, 1915.
5. Einthoven: Le Telecardiogramme, Arch. internat. de Physiol. **4**:149, 1907.

when an electrical tension is present in the heart is similar to the distribution of potential in an equilateral triangle of good conducting material when a potential difference has been developed very near to its geometrical center. Right arm, left arm and left foot (or right foot) represent the corners of the triangle. If we accept this assumption of Einthoven's as representing the actual conditions sufficiently accurately, it is possible to devise a method whereby we can tell just what direction the potential difference in the heart has at any given moment, and also to determine a derived value of the electromotive force in the heart, the so-called "manifest value," a value which bears a constant relation to the actual potential difference in the heart and which changes in value in exact ratio to the change in magnitude of the actual potential difference produced in the heart during each cardiac cycle.

The distribution of potential in an equilateral triangle is very simple if a potential difference has been produced at two points lying very close to its geometrical center. If we lead off from the three corners of the triangle, then the potential differences between any pair of corners is to the potential difference between any other pair of corners as the projection of a line having the direction of the potential difference at the center on the side of the triangle lying between the first two corners is to the projection on the side of the triangle between the second pair of corners; for example, in Figure 3, if we produce a potential difference having the direction $A \rightarrow B$ in the middle of the equilateral triangle $R\ L\ F$, then the potential difference between $R$ and $L$ is to the potential difference between $R$ and $F$ as the length of the line $A_1\ B_1$ is to the length of the line $A_2\ B_2$.

We can find the real direction of the electrical tension in the heart at any phase in its activity from the synchronous heights of the electrocardiograms in two leads, and we can determine the magnitude of the potential difference in the heart as manifested at the body surface at this moment, if Einthoven's equilateral triangle assumption is correct. If we examine the equilateral triangle (Fig. 3) we can see that the lines $AC$ and $Ad$ are parallel and equal to the lines $A_1\ B_1$ and $A_2\ B_2$, and that the perpendiculars dropped from their ends cut one another in $B$. This rule holds for all possible directions of $A\ B$. If we draw (Fig. 4) two lines enclosing an angle of 60 degrees between them and make the ratio of the lengths of these lines the same as the ratio of the potential differences in lead I and lead II, let perpendiculars fall from their ends $D$ and $C$, and connect the point of intersection $B$ with $A$, then $AB$ has the direction of the potential difference in the center of the equilateral triangle, therefore in the heart. The length of the line $AB$ corresponds to the "manifest value" of the actual potential

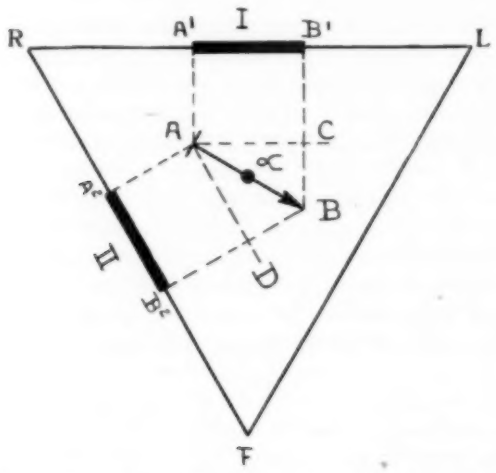



Fig. 3.—The equilateral triangle scheme. R= right hand. L= left hand. F= foot. AB= vector of potential difference in heart. $A_1B_1$= projection of AB on RL. Corresponds in length to the relative value of lead I. $A_2B_2$= projection of AB on RF. Corresponds in length to the relative value of Lead II.

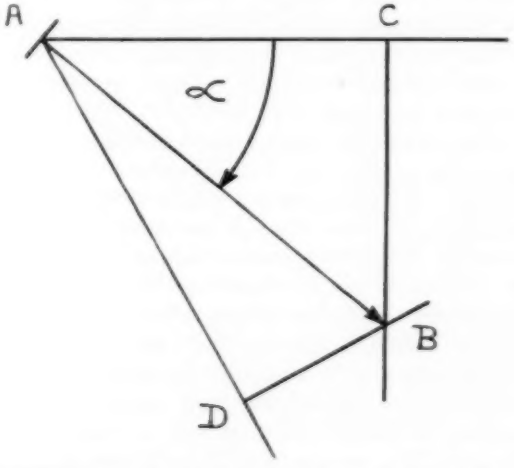



Fig. 4.—Construction of direction and "manifest value" of a potential difference in the heart. AC corresponds in length to Lead I. AD corresponds in length to Lead II. AB corresponds in length and direction to "manifest value" of heart potential.

difference present in the heart, for Einthoven defines the "manifest value" of the potential difference actually present in the heart as the value which is found in one of three leads when the direction of the current between the leading off points is parallel to the direction of the potential difference in the heart. The length of the line *AB* must correspond to the "manifest value" according to the above definition, because the projection of *AB* upon a side parallel to it is exactly equal to *AB*. Or, perhaps, it will be clearer if we think of the potential difference at the center of the equilateral triangle with the direction *AB* and with a value for lead I = $A_1$ $B_1$ gradually turning into a position parallel to *RL*. In this case the value of lead I will come to equal the length *AB*. The "manifest value" is a very important magnitude. In each person there is a definite and constant relation between the actual potential differences existing at the points of production in the heart muscle and the "manifest value" as determined above. We shall probably never learn the actual value of the potential differences developed in the heart muscle. The values obtained by placing electrodes directly on the heart are just as much derived values as those obtained by leading off from the limbs. The electrical potentials present at two points of the heart's surface are due to the algebraically added potentials produced by points of activity throughout the whole heart in exactly the same sense as the electrical potentials present in the limbs are due to the algebraically added potentials produced by these same points of activity. The "manifest value" has a constant relation to the actual potential difference in the heart and therefore may be used as a measure of the actual potential difference. The actual potential difference in the heart varies from moment to moment throughout the heart cycle according to exactly the same curve as the "manifest value." To avoid any misunderstanding it is necessary to state here that the "manifest value" as determined above is the frontal projection "manifest value." If the heart turns about an axis, the frontal plane projection will vary if the axis of rotation is not perpendicular to this plane. The determination of the "manifest value" is just as important in analyzing the spread of the excitation wave in the heart as the determination of the direction of the potential difference.

The angle between the direction of the actual difference in the heart and the horizontal line connecting the points of attachment of the two arms to the body has been called $\alpha$ by Einthoven. It is the angle between *AB* and *AC* in Figures 3 and 4. $\alpha$ is defined positive for the first 180 degrees in clockwise rotation from the direction of *AC*, and is defined negative for the first 180 degrees in anticlockwise direction from *AC*.

The procedure of the author for finding the direction of the potential difference in the heart and its "manifest value" is as follows. An angle of 60 degrees is constructed. Along the horizontal side of the angle a distance equal in centimeters to the value of lead I in tenths of millivolts is layed off. Along the other side of the angle a distance is layed off whose length in centimeters equals the synchronous value of lead II in tenths of millivolts. Perpendiculars are dropped from the end of these lines. The point of intersection is connected with the vertex of the angle. The length of this line in centimeters gives the potential difference corresponding to the "manifest value" for this moment in the cardiac cycle, the direction of this line gives the direction of the resultant electromotive force present in the heart at this moment and the angle formed by this line with the horizontal line is the angle $\alpha$.

The schema of the equilateral triangle was only an assumption when propounded by Einthoven. In 1914 I carried out some experiments in the clinical laboratory of the department of internal medicine of the University of Giessen with Professor Weber which demonstrated that the Einthoven assumption was accurate enough for purposes of electrocardiography. Electrodes were placed in the heart of bodies which were waiting for necropsy. The electrodes were isolated, except where they entered the heart. Potential differences were developed in the heart by means of a storage battery connected to the electrodes. By means of two string galvanometers the potential differences of lead I and lead II were recorded. The electrodes were given various positions in the heart so as to produce various directions of potential difference in the heart. These directions were determined for each position of the electrodes and the angle $\alpha$ thus measured compared with the angle $\alpha$ constructed from leads I and II by our method. There was usually an agreement of better than 10 degrees between measured and constructed directions of the potential difference in the heart. In one case the measured and constructed direction of potential differed by about 20 degrees. These experiments showed that Einthoven's schema of the equilateral triangle is apparently accurate to $\pm$ 10 degrees, an accuracy sufficient for practical purposes. These experiments were carried out on only two cadavers, but we believe that they demonstrated for the first time that Einthoven's schema of the equilateral triangle is apparently accurate to $\pm$ 10 degrees. We can, therefore, make use of the method for determining the direction and "manifest value" of the electromotive force developed in the heart during the heart's activity.

It is necessary to emphasize that only synchronous points in the three leads may be used for the construction. It is not permissible to use the peaks of the *R* waves in two leads. A difference of 0.01 second in the phase of the ordinates may cause an error of 60 degrees in the determination of the direction of potential in the heart. The *R* peaks in the various leads are almost never synchronous as the reader will immediately appreciate when he considers that the R peaks repre-

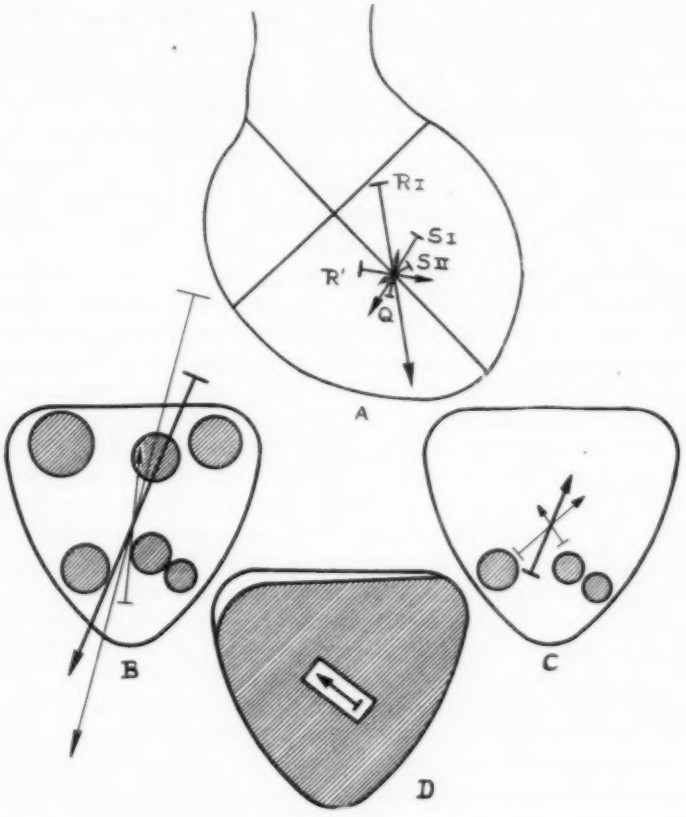



Fig. 5.—A. Orthodiagram of normal heart with vectors of potential corresponding to various points of electrocardiogram. B. Direction of potential difference when all the subendocardial area of apex is electronegative and most of the basal subendocardial area is negative at time of R peak. C. Direction of potential difference when areas about three papillaries are electronegative at time of Q wave; the right papillary in this case having received the negative wave first because of shorter path. D. Direction of potential when all of the heart muscle is negative (both Purkinje and ordinary heart muscle) except a small volume of muscle about the right base.

sent the maximum projections of a rotating vector of potential upon three lines whose directions vary by 60 degrees. It is often of advantage to use leads I and III or leads II and III instead of leads I and II in constructing the vectors of potential difference in the heart. A glance at Figure 3 will show how the construction is made in each of these cases.

Figure 5 is the orthodiagram of a normal heart in which arrows have been drawn to represent the direction and "manifest value" of the electromotive force in the ventricle at five different phases of the ventricular systole. These arrows were constructed according to my method and drawn through a point in the orthodiagram assumed to be close to the center of gravity of the ventricular mass. The arrow marked $Q$ was constructed from synchronous points on the two electrocardiograms corresponding to the apex of the $Q_I$ wave. The arrow $R^1$ represents the direction and "manifest value" of the potential difference in the heart 0.01 second later and the arrow $R_I$ represents the direction and magnitude corresponding to the peak of the $R_I$ wave about 0.02 second after the $Q$ wave. The arrow $S_I$ was constructed for a period corresponding to the apex of the $S$ wave in lead I nearly 0.02 second after the $R_I$ peak. The apex of the $S$ wave in lead II was reached somewhat later, at which time the vector representing the direction and "manifest value" of the electrical tension in the heart is the arrow $S_{II}$. These arrows are sufficient to give us an idea of how the excitation wave spread over the ventricle of this heart. The first signs of ventricular negativity is the $Q$ wave. This is the moment when the excitation process coming down the His-Tawara bundle shoots into the ventricles in areas of the subendocardium close to the three papillary muscles, the right papillary and the anterior and posterior of the left ventricle. The direction of this arrow indicates that the preponderance of negativity at this moment is on the right side and more toward the apex than the base of the ventricles. The distance traveled by the negative wave along the right bundle branch to the point at which it spreads out in the subendocardial layers of the right ventricle is less than the distance traveled along the anterior papillary and the posterior papillary branches of the left ventricle to the points at which these branches merge into the subendocardial layers of the left ventricle. The right ventricle is negative a short time before the left.

Figure 5° is a graphical representation of the frontal projection of a heart and the areas of excitation at the period of a heart's cycle represented by the $Q$ wave. In the right ventricle there is an area somewhat larger than either of the areas in the left ventricle. Assuming that the velocity of the excitation wave in the subendocardial

layers is two and one half meters and that the path to the two papillary muscles in the left ventricle is about one centimeter longer than to the papillary in the right ventricle, the size of the circles represents exactly the size of the areas in excitation about the right papillary and the two left papillary muscles. The two short arrows represent the vectors of potential for the two ventricles and the long arrow represents the resultant potential difference in the heart. The apical subendocardial layer in the right ventricle is practically all in excitation at this moment. In about 0.004 second more the whole of the apical subendocardial layer in the left ventricle will be saturated with negativity.

About 0.01 second later the "manifest value" has increased and the vector has rotated into position $R^1$. This could only be brought about by an increase in negativity at the bases and an increase in the spread of the negativity in the left ventricle. In other words, the negativity is spreading out in the subendocardial layers of the conducting system toward the base and in the left ventricle the lag due to the increased length of path is being overcome. About 0.01 second later the arrow indicating the direction and "manifest value" of the potential difference in the heart has the direction and length $R_1$. In other words, electronegativity has increased more rapidly at the base than the apex, and more rapidly in the left ventricle than in the right; the center of electrical mass is in the base of the ventricles a little more toward the left side than the right side of the heart.

Figure 5[b] is a graphical approximation of the relation of the excited or negative areas in the heart at a point in the heart cycle represented by the $R_1$ peak. The subendocardial apical areas are all negative now and the basal areas of the subendocardium in both ventricles are also nearly saturated with negativity. The amount in the left ventricles predominates slightly. The $R_1$ peak represents a point in the cardiac cycle about 0.03 second after the beginning of negativity in the ventricles. The path to the left ventricles is perhaps slightly longer. If we assume it to be one centimeter longer, the negativity gets into the left ventricle about 0.004 second after it has reached the right ventricle. But the spread toward the bases of the ventricles has an advantage in the left ventricle, namely, there is a spread from two separate areas, the areas about the two papillary muscles of the left ventricle. In some cases this advantage in accelerating the spread of the negative wave in the left ventricle will more than overcome the disadvantage due to the negativity reaching the left ventricle a very short time after it reaches the right ventricle. This may be the explanation of the direction of the vector $R_1$. The size of the circles in this figure were determined by considering the heart to be a very simple geometric figure

and using orthodiagraphic dimensions for calculating the size of the internal areas of the ventricles. Of course the figures are merely graphical schemes to aid the imagination. It still remains for some one to make geometrical studies of the form and dimensions of the ventricles and their topographical relation in space.

The reader who has followed the reasoning employed in the discussion of the elementary cases in the first part of this paper will inquire how the base can become more negative than the apex if the negativity first reached an area nearer the apex than the base. There are a number of possible explanations for this. The center of gravity is determined by the distribution of muscle mass in space. The heart can be likened to a hollow cone with a partition in it. If the walls of this hollow cone were of equal thickness on both sides of the partition, and if the partition lay in the sagittal plane of the body it would be a simple matter to find the center of gravity by mathematical procedures. As it is, we can only say about where the center of gravity lies. It must be somewhere between the upper third and lower half of the septum and toward the left side of the septum. A plane passed through the center of gravity parallel to the base will divide the heart into two muscle masses which, when negative, gives rise to potential differences of equal "manifest value" and opposite direction. Because of the geometrical form of the heart, the area of the subendocardium corresponding to the apical muscle mass will be smaller than the area of the subendocardium corresponding to the basal muscle mass.

The excitation wave has a velocity in the subendocardial specific conducting layers which is from five to ten times the velocity in the heart muscle fibers themselves.[3] The excitation process enters the apical side of the subendocardium first, causing preponderance of apical negativity, and it spreads throughout the apical subendocardial layer at a velocity of from two and one half to three meters per second. At the same time it is spreading toward the base at the same rate. The whole of the subendocardial apical area is negative first, and from here the excitation process travels into the real muscle fibers. But it spreads here at a very slow rate, and very probably there is also a short pause for the transition so that in a very short period of time the whole of the basal subendocardial layer is negative, and as this area is larger than the apical area there is more electronegativity at the base than apex.

The *R* peak would, therefore, indicate approximately the end of the spread of excitation on the inside of the heart. From this point on, the electronegativity spreads from within outward. About 0.015 or 0.02 second after the *R* peak the *S*1 peak is reached. The arrow *S*1 indicates the "manifest value" and direction of potential at this

moment. The rotation of the vector from $R_I$ to $S_I$ can only be brought about by an increase in apical negativity of such magnitude that the base is now only a very little more negative than the apex. Just how the apical negativity increases so much more rapidly than the basal at this point can only be inferred. One assumption is that after the subendocardial layers become negative there is a slight pause in the spread of the excitation process from the peculiar Purkinje fibers into the heart muscle fibers. This would be analogous to what always happens when the excitation process passes from one kind of tissue into another. If this assumption is in accordance with the facts, then as the apical subendocardial layer of specific conducting fibers became negative a little sooner than the basal subendocardial area, the excitation process would pass over into the ordinary muscle fibers of the apex about as far ahead of the excitation process in the ordinary fibers at the base as the excitation process in the apical subendocardial area was ahead of the excitation process in the Purkinje system at the base. This assumption, which appears plausible, would explain very nicely the rotation of our vector toward the apex and the production of the S wave in lead II. If our assumption is correct, the peak of the *R* marks the beginning of the spread of the excitation process in the real heart muscle fibers and in areas nearer the apex than the base of the heart.

The arrow $S_{II}$ is the vector for a point in the heart cycle about 0.01 second after $S_I$. The arrow has rotated still farther toward the apex. At this point the "manifest value" is very small, showing that nearly all of the heart muscle is negative or excited with just a little more apical basal muscle in excitation. With the spread of the negativity to the remaining basal portions the spread of the excitation process is complete. The whole heart is negative and the resultant potential difference in the heart is zero. The galvanometers indicate no current.

We have attempted a graphical representation of the excited heart muscle in Figure $5^d$ corresponding to the $S_{II}$ peak. A small rim of heart muscle toward the base a little larger on the right side is still unexcited. An explanation for this can be found in the fact that the path of conduction in the subendocardium to the base is the longest path, and therefore the heart muscle fibers here receive their negativity from the Purkinje system last. We have assumed that the negative process in the basal subendocardial areas of the Purkinje system on the right side of some hearts lags a little behind the area on the left side because the negativity spreads from two points in the left ventricle. Because of this the spread of negativity in the uppermost portions of the basal heart muscle on the right will lag a little behind the spread on the left side in these hearts.

This analysis of the spread of the electronegative wave in the heart is in good accord with the known facts of the physiology of the heart. Garten[6] has shown that if the intraventricular pressure in the left ventricle of the dog is recorded with a very sensitive manometer of extremely slight inertia and great speed of reaction,[7] the first indication of pressure development in the left ventricle comes about 0.025 second after the beginning of the ventricular electrocardiogram and just before or just after the peak of the *R*. The pressure developed is at first very slight and becomes more marked farther down the catacrotic limb of the *R*. The maximum of intraventricular pressure is reached very shortly after the *QRS* group is complete. These curves of Garten suggest that small portions of the heart muscle are in contraction 0.015 second after the peak of the *Q* is reached and just before or at the *R* peak, and that the greater part of the heart muscle is in contraction by the time the *S*II peak is reached and before the end of the *QRS* group. The small "initial vibrations" of the first heart sound also appear about 0.03 second after the beginning of the ventricular electrocardiogram and before the *R* peak or just after the *R* peak.[8] The large vibrations of the first heart sound comes about 0.04 second after the beginning of the ventricular electrocardiogram, or about 0.01 second after the *R* peak and before the *S*II peak.

The early slow and slight rise in Garten's intraventricular pressure curves and the "initial vibrations" of the first heart sound curves are best explained as due to the contraction of the papillary muscles. These muscles receive their excitation before the rest of the heart muscle, during the *Q* wave period and as the contraction of the heart muscle begins not later than 0.004 second after the electronegative wave reaches it,[9] the papillary muscles are probably well in contraction 0.03 second after the beginning of the ventricular electrocardiogram. Using 400 centimeters per second as the velocity of the propagation of the negative process in the ordinary heart muscle fibers, we calculate that the greater part of the papillary muscles must be in contraction 0.03 second after the electronegative process reaches their bases. All the data at hand therefore agree very well with our interpretation that the *Q* wave represents the spread of the excitation process in the subendocardial Purkinje system of the apices.

The anacrotic limb of the *R* wave starts before the initial vibrations

6. Garten: Ztschr. f. Biolog. **66**:23, 1915.
7. The period of these manometers is only 0.003 second.
8. Bull: Quart. J. Exper. Physiol. **4**:289, 1911. Fahr: Heart **4**:147, 1912.
9. Kahn: Arch. f. d. ges. Physiol. **132**:209, 1910. Garten: Loc. cit.

or the earliest indication of pressure development in the ventricles. The beginning of the *R* wave, therefore, does not represent the negativity of the ordinary muscle fibers of the papillary muscles to any great extent. It must represent some other process. The direction of the vector of potential indicates that the process is spreading toward the base of the heart. The anacrotic limb of the *R* is very probably associated with the spread of the negative process in the subendocardial Purkinje system toward the bases of the heart. Of course, there is negativity in the ordinary muscle fibers of the papillaries before the *R* peak is reached. But the papillaries are attached at points not far below the center of mass of the heart and their upper end extends toward the bases. When all parts of the papillary muscles are negative, the total effect on the direction of potential in the heart will be insufficient to neutralize the effect of the preponderance of subendocardial basal negativity.

The large vibrations of the first heart sound and the sharp rise in Garten's intraventricular curves, which come about 0.01-0.02 second after the *R* peak, are an indication that fairly large portions of the heart musculature are in contraction just before the *S* peak is reached. If we bear in mind that even with the most delicate apparatus the mechanical activity of heart muscle lags 0.004 second behind the electrical activity, we can come to no other conclusion than that the catacrotic limb of the *R* represents very closely the moment when the electrical activity of a large part of the ventricular musculature begins. As our analysis shows that this catacrotic limb of the *R* indicates the development of electric negative potential toward the apex, it is very probable that the down stroke of the *R* to the *S* peak represents electrical activity beginning in the ordinary muscle fibers of the apex of the heart and spreading toward the base.

Before proceeding any farther, we wish to emphasize that the *R* peak does not mark the beginning of the spread of the excitation in the ordinary muscle fibers of the apex sharply. The negative process coming down the main branches of the His-Tawara system enters the ventricle at very small areas from which points the spread in the subendocardial layers will proceed in all directions in such a way that the increase in negativity will be very nearly proportional to the squares of the time. The curve of the spread of negativity in the ordinary muscle fibers of the heart will follow the form of the curve for the Purkinje system very closely. The reader who is familiar with the graphs of functions will readily see how the curve representing the spread of apical negativity in the ordinary muscle fibers if it starts at a point a little before the time marked by the *R* peak will only cause a little

flattening of the curve representing the resultant potential in the heart at first, but that as the negative process spreads more rapidly with time at about the moment marked by the R peak the resultant curve will begin to take a different direction.

We have not as yet taken into consideration the fact that the maximum of negativity at a point is not present instantaneously but needs a short time for full development. This fact would not cause any modification of our views, as the time for full development of electronegativity at a point is very short and would only tend to prolong the electrical curve for a given set of fibers farther into the curve for a succeeding set and into the curves of mechanical activity. Thus the end of the anacrotic limb of the *R* would represent further development of negativity at points of the basal subendocardium which had received their electronegativity a short period before.

There is one more test of the plausibility of our interpretation. Lewis and Rothschild[3] have shown that the velocity of conduction in the Purkinje system is about from 2.5 to 3 meters per second, and about 400 millimeters per second in the ordinary muscle fibers of the heart. Measurements of the distance from the point where the His-Tawara system spreads out into the arborizations of the Purkinje system to the farthest point on the subendocardium of the apical layer give a conducting path of about 3 cm. It would take the electronegative wave about 0.01 second to reach all parts of the apical subendocardial Purkinje system. From the beginning of the ventricle electrocardiogram to the *Q* peak is from 0.01 to 0.015 second, a result which agrees very well with the above measurements. The distance from the base of the papillary muscles to the farthest points in the basal subendocardium in normal hearts is from 6 to 8 cm. This would give a conduction time of about 0.025 or 0.03 second. From the beginning of the ventricle electrocardiogram to the peak of the *R* is about 0.03 second. Another very good agreement of the facts of velocity of conduction and distance of conduction with the interpretation of the *R* which we have given. The thickness of the basal musculature can be taken as 12 mm. in the thicker parts. This would require 0.03 second for conduction of the wave from within outward. From the *R* peak to the end of the *S* wave are 0.03 or 0.04 second. Another good agreement of the "interpretation of the *S* wave with the experimental facts. The calculated times of conduction are all slightly shorter than the corresponding time as derived from the *R* peak and the end of the *S* wave. This is probably due to the fact mentioned above, that the negativity takes a short time to develop to its maximum at a point.

According to our analysis of this electrocardiogram which has an *S* wave in lead II, and where the vector corresponding to $S_{II}$ indicates greater negativity at the apex of the heart than at the base, the base must receive the last increment of action negativity. This fact of the negativity appearing last at the base is in good accord with Einthoven's explanation of the *T* wave.

For a short period following the *S* wave there is no resultant potential difference in the heart despite the fact that the whole of the heart is in activity. This we have already explained as due to the fact that the summation of all the potential differences throughout the whole muscle mass when added as vectors must be zero. There is, therefore, no potential difference produced in parts external to the heart. The *T* wave indicates that there is a resultant potential difference present in the heart within a very short interval following the *S* wave. We shall follow the Einthoven[10] view in explaining the *T* wave. The view held by some that the *T* wave is related to the contraction of the muscle and the *QRS* group to the spread of the excitation process is not in accord with the facts for the contraction process begins a few hundredths second before the *T* wave and the ventricle pressure curve shows a relaxation of the contraction just about where the *T* wave starts.

Some have thought that the *T* wave was the expression of a different process, for example, a metabolic process. This again does not agree with the facts, for we would expect the metabolic process associated with the heart's contraction to precede the contraction or to follow it. The *T* wave begins after the contraction process and ends just a moment after the second sound.

In our opinion Einthoven's explanation is the only logical one. According to Einthoven, the negative process after reaching its maximum about the end of the *QRS* group begins to die out. It dies out more slowly in certain parts than in others, and thus leaves a residual preponderance of negativity at the parts where it begins to decrease last. The decrease in negativity will be a much slower process than the increase. All curves of muscle activity, whether of the action current or the contraction process, show a sharp rise, a short period of maximum and a slow decline of the curve to the initial position.

If we think of our orthodiagram of the ventricle as divided by a horizontal line *PR* running through the center of gravity (Fig. 6) and the arrow as representing the resultant potential differences in the two parts, these arrows have opposite directions and equal lengths during the period following the *QRS* group and before the beginning of the *T* wave, for the resultant electromotive force in the whole heart is zero

10. Einthoven: Arch. f. d. ges. Physiol. **122**:517, 1908.

at this time. If we assume the negativity now begins to die out in the lower portion of the heart projection, we may draw the curve *ABC* shown in Figure 7 to represent the dying out of negativity in the apical portion. About 0.02 second later the negativity begins to decrease in the basal portion according to the curve *HDE*. The difference in the ordinates of these two curves is the curve *FTG*.[11] The curve *FTG* approximates very closely the *T* wave of the electrocardiogram in lead II of the heart, whose orthodiagram and electrocardiagrams have been used for this analysis of the spread of the excitation process in a normal heart. The construction of Figure 6 was determined as follows. The

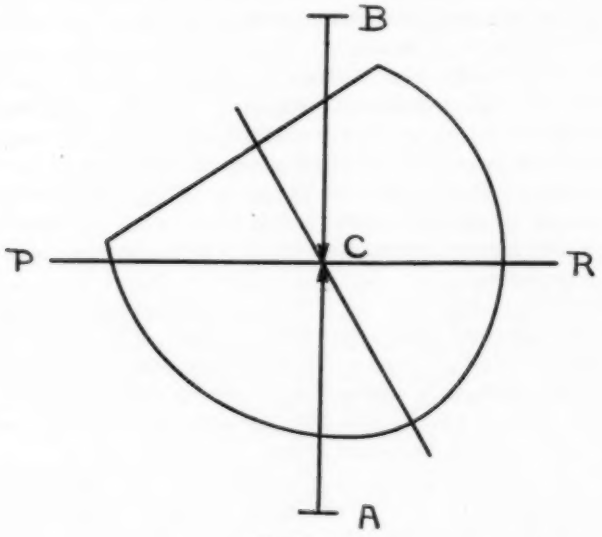



Figure 6.

direction of potential difference in the heart was found for a number of points on the *T* wave in lead I and lead II. The values of an angle $\propto$ for various points lay between 82 and 93 degrees. The angle $\propto$ for various points along the *T* wave is not constant, but if we select an angle $\propto$ equal to 86 degrees it will represent the direction of potential in the heart during the period of time in which the *T* wave is recorded with sufficient accuracy for every practical purpose. The angle made by the arrow *BC*, shown in Figure 6, with the line *PR* is an angle $\propto$ equal to $-86$ degrees and the angle $\propto$ made by the arrow *AC* with the line *PR* equals 86 degrees.

11. In order to make the curve *FTG* large enough for publication we have multiplied the differences between the ordinates of *ABC* and *HDE* by 4.

In constructing Figure 7 it was necessary to find two curves, *ABC* and *HDE*, which would represent the disappearance of negativity in the two portions of heart muscle in such a way that when the one curve, *HDE*, begins about 0.02 second after the other curve, *ABC*, the difference in their ordinates makes a curve closely approximating our *T* wave. In the drawing the distance between the ordinates equals 0.020 second, and between the abscissae 1 millivolt. The ordinates of the curve *FTG* are 1 millivolt equal to the distance between 4 abscissae. This change in scale was only necessary in order that the *T* wave reproduce large enough. We wish to emphasize that our construction is purely hypothetical and based on Einthoven's explanation of the *T* wave. This explanation is the only one which is in accord

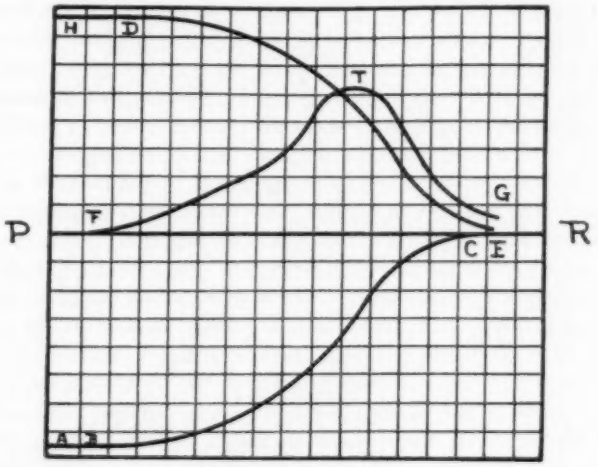



Fig. 7.—ABC is the curve of disappearance of negativity in caudal portion of heart represented in Figure 6. HDE is the curve of disappearance of negativity in the portion of the heart above line PR of Figure 6. FTG is resultant potential difference in heart found by adding ordinates of ABC and HDE, and multiplying by four in order to make FTG large enough to show well in the reproduction.

with all the known facts of physiology, and for the present should be used as a working hypothesis. Mines[12] has shown that by heating the apex of the tortoise ventricle he could shorten the period of apex negativity. In the tortoise heart the *T* wave was negative before heating, and after heating it became upright and had the form of the *T* wave of the human electrocardiogram. Thus by prolonging the base negativity he got the type of *T* wave shown in the normal human

12. Mines: J. Physiol. **48**:242, 1913.

electrocardiogram. This seems to be very good experimental evidence for the correctness of the explanation represented in Figure 7. If it were possible to cool the apical portion of the heart represented in Figure 6, thus prolonging the negativity in this portion and in consequence both shifting the curve *ABC* in figure 8 to the right and reducing its slope, we would get a negative *T* wave in the resulting electrocardiogram.

The electrocardiograms of five normal hearts have been analyzed by the above method and the same type of propagation of the electronegative process has been determined for all. It so happened that all of the synchronous records taken by us showed *Q* waves in leads II and III, and *S* waves in leads I and II. A *Q* wave in lead I would be associated with a shorter path to the left ventricle than the right ventricle, or a position of the right papillary to the left of the center of mass. We are not in possession of an electrocardiogram showing this type of propagation in a normal heart, but we have seen them in the collections of other electrocardiographers. Some electrocardiograms from normal hearts apparently show no *S* waves in leads I and II. We need not infer a fundamentally different type of propagation for these cases. Either the vector representing apical preponderance of negativity lies in or nearly in a sagittal plane and therefore has little influence on our frontal leads or the spread of negativity from the apical Purkinje system into the ordinary muscle fibers is so little ahead of the spread into the basal muscle fibers that the net result is simply a rapid descent of the *R* wave with a gradual decline in its gradient toward the end. In other words, the apical muscle fibers receive their negativity first, causing a neutralization of the basal negativity due to the excitation in the basal Purkinje system, but the ordinary basal muscle fibers receive their negativity also a very short time after the apical, and in this case the lag of negativity at the base is so small that the sharp descent of the *R* is soon changed into a less steep gradient and does not end with an *S* wave.

Some electrocardiograms do not show a *Q* wave in leads II or III. In these cases we infer that the papillary muscles lie high up on the ventricle walls so that the spread of negativity toward the base is more rapid than toward the apex.

Figure 8 is the orthodiagram of a heart showing left ventricular dilatation and hypertrophy in a patient suffering from myocardial degeneration. The electrocardiogram was the typical electrocardiogram of so-called left ventricular preponderance; high $R_{I}$ and deep $S_{III}$. The term "left ventricular preponderance" does not apply to the electrocardiogram as the arrows in Figure 8 show, for they indicate that the characteristic form of this electrocardiogram is determined

by a preponderance of electronegativity in the right side of the heart. This is to be explained as follows: The dilatation and hypertrophy of the left ventricle cause an increase in the normal length of the His-Tawara bundle branches in the left ventricle. The increase in length of conducting path is accompanied by increase in time of conduction to the left ventricle. The right ventricle, therefore, gets its negativity 0.01 or 0.02 second earlier than the left ventricle, and this determines the direction of the vector. As the left ventricle increases in negativity it merely compensates the right ventricular preponderance until the moment when the whole of the right and left ventricles are negative and the resultant vector is zero.

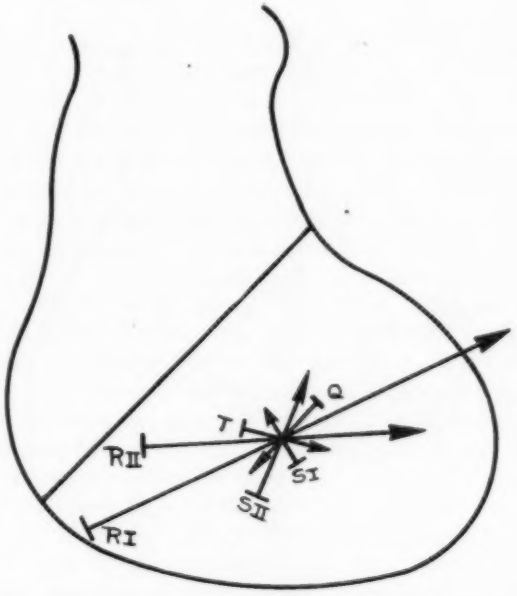



Fig. 8.—Orthodiagram of heart with predominating left ventricular enlargement with vectors of potential corresponding to various points on electrocardiogram.

In Figure 8 it will be seen that *Q* indicates negativity of the left side of the heart. We are at present unable to explain this, excepting on the assumption that in this case the dilatation and hypertrophy took place in such a way that the right papillary muscle came to have a position to the left of the center of gravity. If we recall the topography of the heart we see that the septum does not run in a sagittal plane, but in a plane lying between the sagittal and frontal planes.

In other words, the right ventricle overlaps the left to a certain extent in a frontal projection. This overlapping must be increased in certain types of dilatation of the ventricle through the increase in size of that portion of the left ventricle lying behind the right ventricle in frontal projection. The right papillary muscle comes off the septum near its anterior border. It could very well be, that in certain forms of dilatation of the left ventricle, the right papillary muscle comes to lie to the left center of gravity of the heart muscle mass. From this point the negative process spreads throughout the right ventricle a little ahead of the spread in the left. We would then get vectors corresponding to those in Figure 8, which is not a pure left ventricular dilatation. The patient was decompensated and showed signs of beginning relative mitral incompetence.

We have analyzed about twenty electrocardiograms of patients with systolic blood pressures ranging from 250 to 320 mm. of mercury. At the time the records were made none of them showed signs of mitral incompetence, and the roentgen rays indicated that the increase in size of the heart was due very largely to dilatation and hypertrophy of the left ventricle. The electrocardiograms of all showed a high $R_{I}$ and deep $S_{III}$ and the construction of the direction of potential difference in the heart showed that the form of the electrocardiograms was due to a preponderance of electronegativity in the right ventricle throughout the period of the *QRS* group due to increase in length of the path of conduction on the left side. Most of these cases showed no *Q* as in Figure 8, the arrows pointing toward the left from the moment that the excitation process got into the ventricles.

To my mind there is no question that the form of the electrocardiogram in pure left ventricular dilatation and hypertrophy always shows a high $R_{I}$ and deep $S_{III}$, and an analysis shows that in these cases the form is due to preponderance of right ventricular negativity. In Figure 8 the potential difference $R_{II}$ was present in the heart about 0.01 second after *Q*. $R_{II}$ was followed by $R_{I}$ in about 0.01 second. $S_{II}$ followed in another 0.02 second and $S_{I}$ in another 0.01 second. The duration of the *QRS* group from the beginning of the ventricle electrocardiogram to the point where the catacrotic limb of the *S* ended was 0.08 second. In most of the electrocardiograms of pure left ventricular enlargement of our collection the duration of the spread of negativity in the ventricles is longer than this, from 0.10 to 0.12 second. This increase in length of time of the propagation of the excitation process in these hearts must be ascribed to the lengthening of the path in the left ventricle and in the increased thickness of the walls. Most of the electrocardiograms of predominating left ventricular enlargement in our collection have negative *T* waves in lead I

and positive *T* waves in lead III. This indicates that the negative process lasts longest at the left base, and we can infer from this that the left base received its negativity last. Of course we can not infer too much from the T wave in these hearts, for the musculature is no longer normal in them.

Just as our construction of the direction of the potential difference in the heart has shown that it is the preponderance of right ventricular negativity that determines the form of the electrocardiogram in pure left ventricular enlargement due to an increased length of the path of conduction in the left ventricle, so also our analysis of electrocardiograms from bundle branch lesions has shown us that the prevalent

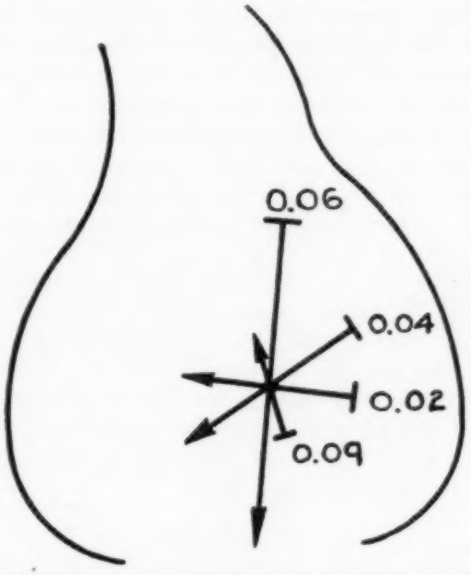



Fig. 9.—Orthodiagram of heart with mitral stenosis and tricuspid insufficiency with vectors of potential corresponding to various points on electrocardiogram. Time in seconds after onset of ventricular electrocardiogram.

conceptions here also are wrong. A high *R*I and deep *S*III means left bundle branch block, for the vectors show that the right heart is negative first and that as the left heart becomes negative the right sided preponderance is neutralized and the resultant approaches zero. Vice versa, a high *R*III and deep *S*I in bundle branch block indicates right bundle branch lesion for the construction of the direction of the potential difference in the heart shows that the left side is negative first and the vector is swung toward the right about 0.05 or 0.06 second after the beginning of the electrocardiogram.

In a purely right ventricular dilatation and hypertrophy the electrocardiogram shows a deep $S_I$ and high $R_{III}$. In case there is both left and right sided enlargement the same is true, provided that the right sided enlargement is greater than the left sided enlargement. Construction of the direction of potential in the ventricles shows that in these cases the left side of the heart is negative first and that the right ventricle receives its negativity later because the increase in size of the right ventricle necessitates a greater length in the right bundle branch and in the path of the spread in the subendocardial system of Purkinje fibers. Figure 9 is the orthodiagram from a case of mitral stenosis with relative tricuspid insufficiency. Into the roentgenogram of the heart the arrows have been drawn as usual. In this drawing the negative ends of the arrows are not marked as $Q$, $R$ and $S$, but the time after the beginning of the ventricle electrocardiogram has been used to designate the arrows. The negativity begins in the left ventricle toward the apex and then spreads to the left base. The velocity of the propagation is very slow, probably both because of the increased length of path and because the heart muscle has been damaged. Necropsy measurements of the length of the right bundle branch down to near the papillary muscle showed it to be about 2 cm. longer than either of the left bundle branches. In other words, the left heart receives its excitation wave about 0.01 second before the right ventricle. The average of measurements from the neighborhood of the papillary muscles to the base of the heart showed that the path in the dilated right ventricle was about 3½ cm. longer than in the left. These measurements show that the left side of the heart must get its negativity first, and that in so-called "right ventricular preponderance" we really have a left ventricular preponderance of action negativity shown in the electrocardiogram.

## CONCLUSIONS

1. The method of the equilateral triangle is sufficiently accurate for determining the frontal plane projection of the direction of the potential difference in the human ventricle and its "manifest" or maximum derived value.

2. It is possible to follow the spread of the excitation process throughout the ventricles by following the change of direction of the vector of potential difference throughout a heart cycle and by making use of our knowledge of the architecture of the His-Tawara-Purkinje system, of the approximate rates of conduction of the negative process in this system and in the ordinary muscle fibers and of the time of onset of the first heart sounds and ventricle pressure curve.

3. The excitation process beginning first in the subendocardial layers of the Purkinje system in the neighborhood of the papillary muscles, usually a little earlier in the right ventricle, spreads first to the apical layers causing the *Q* wave. The excitation process is quickly conducted to the basal arborizations of the Purkinje system giving rise to the anacrotic limb of the *R*. While the excitation process is being propagated through the basal Purkinje system the process in the apical area of the Purkinje system is spreading to the ordinary muscle fibers of the apex. By the time the peak of the *R* is reached the negativity in the ordinary muscle fibers of the apex is of sufficient magnitude to neutralize the preponderance in the basal Purkinje arborizations and cause the catacrotic limb of the *R* and the *S* peak. The process meanwhile is passing from the basal Purkinje system into the ordinary muscle fibers of the base. Their negativity increases until the effect of the apical fibers is counteracted and the *S* wave is reduced.

4. The negative process begins to die out at the apex first leaving a preponderance of negativity at the base. This gives rise to the T wave.

5. The form of the electrocardiogram in hearts which have left sided enlargement is due to the increased length of conducting path in the left ventricle. The right ventricle receives its negativity first.

6. In right sided enlargement the left ventricle receives its negativity first because the path of conduction to the right ventricle is longer. The form of the electrocardiogram in these cases is due to a preponderance of negativity on the left side.

7. The diagnosis of right and left bundle branch lesion as commonly made is probably wrong. In left bundle branch lesion we should find a high *R* in lead I and deep *S* in lead III. In right bundle branch lesion we get a deep *S* in lead I and high *R* in lead III.

# A CLINICAL STUDY OF YELLOW FEVER*

## OBSERVATIONS MADE IN GUAYAQUIL, ECUADOR IN 1918

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CHICAGO

The following report is based on the study of about seventy cases of undoubted yellow fever admitted to the lazaretto[1] of Guayaquil, Ecuador, from July to September, 1918. Fifty consecutive cases, including all grades of severity, admitted during the latter part of the investigation, were studied carefully according to a definite plan.

The cases observed by no means represent all the cases that occurred in Guayaquil during the period of study, for not all yellow fever patients were concentrated in the lazaretto by the authorities.

An attempt was made to obtain early cases. One patient was admitted during the first day of his illness, ten hours after an abrupt onset; eleven patients were admitted on the second day, and thirteen on the third day. The others were admitted on various days and as late as the ninth day. Nine cases were considered light and forty-one as severe cases. Eleven patients were admitted in extremis, delirious or comatose.

### EPIDEMIOLOGY

Guayaquil is an endemic center of yellow fever. While no information is available as to the total number of yellow fever cases in the city during the period of this study, there undoubtedly were many cases of all grades of severity. During 1917, 226 patients were admitted to the lazaretto. Of these, sixty-seven died.

The patients in this series were, for the most part, from the poorer classes. Five were soldiers recently recruited from the interior; eleven were servants. There were nine children. The others were

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* Read before the American Society of Tropical Medicine, Atlantic City, N. J., June 17, 1919.

* This clinical study of yellow fever is part of an unpublished report submitted to the International Health Board of the Rockefeller Foundation which appointed the following commission for the study of yellow fever during the summer of 1918: Dr. Arthur I. Kendall, chairman; Dr. Hideyo Noguchi, bacteriologist; Dr. Mario G. Labrado, sanitarian; Mr. Herman E. Radenbaugh, chemist, and Dr. Charles A. Elliott, clinician.

1. The yellow fever hospital is conducted as a part of the sanitary service of the municipality. I wish to express my thanks to Dr. Leon Becerra, director of the sanitary service of Ecuador; to Dr. Wenceslao Paraja, chief of the medical service, and to Dr. Jorge Larrea, director of the laboratories, for daily consultation and advice.

housewives, small shopkeepers, laborers, policemen, etc. A husband and wife, and a brother and sister are included. Of forty-nine patients only two were natives of Guayaquil; nine had lived in Guayaquil for less than two months; the others came principally from the mountain provinces in the interior, eleven from Ambato, seven from Quito, six from Cuenca, four from Latacunga and three from Riobamba.

The houses from which the patients came were found to be quite evenly distributed throughout the city (Fig. 1). In four instances two or more patients came from the same house; a military hospital,

Fig. 1.—Spot map of Guayaquil, showing distribution of forty-seven of fifty consecutive cases admitted to the lazaretto.

a military barracks and two private homes. The homes of the patients were made of cane, wood or corrugated iron, usually two stories high; the ground floor was constructed of mud or wood. About an equal number of patients lived on the ground floor and on the second floor. The type of house seemed to have little influence on the incidence of infection. *None of the houses were screened.* Inquiry showed that mosquitoes, often in great numbers, were present in all of the houses. The common house mosquito, *Aedes calopus*, Meigs (*Stegomyia calo-*

*pus*), was found breeding in these homes. Bedbugs were common and head lice were found on most of the women and children admitted to the hospital. Thirteen of thirty-one patients habitually went barefooted, and many were admitted with numerous sores on the legs from infected mosquito bites.

While the mosquito, *Aedes calopus*, Meigs, has been considered the chief, if not the only, means of transmission of yellow fever, other means, such as direct transdermic infection, seem possible in view of the apparent similarity of yellow fever and infectious jaundice. That there were many habitually barefooted patients with infected sores, and that yellow fever was experimentally produced in animals by Noguchi by inoculations through the unbroken skin, would seem to support this view.

It seems fitting to call attention to the discovery by Noguchi[2] of a minute organism in the blood and tissues of these patients. He has provisionally called the organism the *leptospira icteroides*. He was able to transmit the organism to experimental animals by the injection of blood and of tissue emulsions from yellow fever cases, producing in guinea-pigs clinical and pathologic manifestations similar to those found in the human cases. By special methods these organisms were obtained in pure culture. They resemble the causative agent of infectious jaundice morphologically, but are distinct immunologically. Injections of pure cultures into guinea-pigs produced symptoms and lesions closely paralleling those of human yellow fever. From the blood, liver and kidneys of guinea-pigs inoculated with blood from yellow fever patients, organisms identical with those isolated from human blood were found. The disease was readily transmitted from animal to animal.

### GENERAL CLINICAL DESCRIPTION

The clinical picture of yellow fever as seen in these cases was most striking. Noteworthy were the rapid onset and progress of the disease; the usually low and short fever course accompanied by bradycardia, congestion of the face, sclerae and gums; the subsequent afebrile period of apparent intoxication with increasing jaundice, hemorrhage and nephritis. Prompt death or rapid and complete convalescence resulted. The whole course of the disease was short. The patients who had light infections recovered, on an average, by the end of the first week; the patients who had severe infections recovered by the end of three weeks. In fatal cases death occurred as early as the fourth and as late as the eighteenth day, on the average on the eighth day.

2. Noguchi, H.: Etiology of Yellow Fever, J. Exper. M. **29**:547, 1919; **30**:1, 87, 401, 1919.

Fever was present for the first few days only, as a rule dropping to normal on the fifth, sixth or seventh day. The patients with light infections then recovered rapidly, while those with severe infections were desperately ill during the afebrile period of intoxication.

It seems proper to speak of two periods, first, the period of *invasion*, of four or five days' duration, with fever, congestion, headache, backache, epigastric and general abdominal pain and tenderness, muscle tenderness, nausea and vomiting. During this period the patient is feverish, the face and conjunctivae are suffused; the gums are swollen. The patient is restless and apprehensive. The urine shows increasing evidence of nephritis, with progressively increasing albuminuria and cylindruria. The general congestion gradually gives way to the second period, apparently one of *degeneration*, during which the patient is extremely toxic, relaxed and weak. Jaundice increases to an extreme degree, and nausea with vomiting, often "black vomit," occurs. Hemorrhages occur from any source: gums, gastro-intestinal tract, nose, urinary tract or uterus, and into the skin or conjunctivae. These hemorrhages may be slight and intermittent; as, in the skin, from petechiæ to areas several centimeters in diameter, or occasionally, as epistaxis or nosebleed. The hemorrhages may be continuous and alarming as from the gum edges, nose, or as repeated "black vomit" and melena. There may be free bleeding from an abraded skin surface, from the uterus, or from the urinary tract.

There is much general abdominal tenderness, especially in the epigastrium. The liver edge is exquisitely tender. The patient complains of headache, backache and general aching of the extremities. The stomach is intolerant of food. Persistent vomiting often occurs. Uremic symptoms frequently develop. Diminution of urine or complete anuria occurs, also restlessness, headache, hiccup, delirium, stupor, coma and convulsions. Albuminuria increases to an alarming extent. From a trace of albumin on the second day there may be an increase to 4 or 5 gm. per liter on the seventh day, coincident with intense cylindruria, mostly of granular, blood or epithelial casts, paralleling the albumin. Fetor ex ore may become intense and characteristically the odor of the deadhouse. The pulse is full, soft, slow, frequently dicrotic, becoming fast in extremis.

The patient may die during the second week, apparently uremic, or convalescence may ensue rapidly while the jaundice increases. In the latter event, hemorrhages cease; the gingivitis subsides. All mucous membranes appear jaundiced and anemic; the abdomen is retracted and less tender. The patient appears dried out, emaciated, hungry. Albumin and casts disappear rapidly from the urine. The patient asserts that he is well after two or three days and wishes to be up and

about. Strength and body weight are rapidly regained. Convalescence is rapid and apparently complete in a very few days.

### CLINICAL FINDINGS IN DETAIL

*Anamnesis.*—The symptoms were fairly uniform. In uncomplicated cases, a precipitous onset was the rule. A feeling of uneasiness, particularly in the epigastrium, and aching of the head, back and extremities were first noticed. Fever developed rapidly, often preceded by a chill or chilliness. Nausea and vomiting frequently occurred from the start, the vomit being usually "bilious," although "black vomit" was sometimes present as early as the second day. Fever, headache, backache, general muscular and epigastric tenderness or pain, nausea and vomiting persisted in various combinations until admission to the hospital.

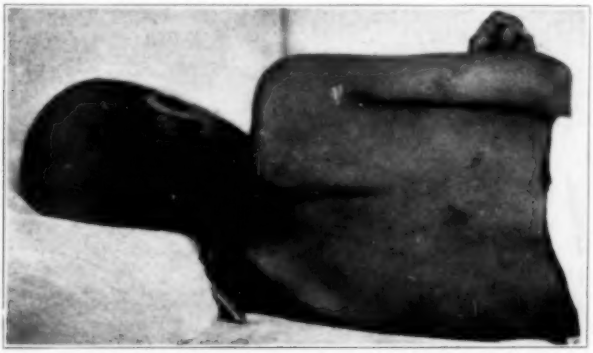

Fig. 2.—Severe case (Case 47) with recovery. Girl, 7 years of age, on fourth day of disease. Multiple hemorrhagic areas into the skin are shown.

Certain patients who had been suffering from malaria for varying periods, gave a history of unusual symptoms, such as the onset of nausea, vomiting, epigastric tenderness, head and backache, and persistent fever. In such cases the diagnosis was uncertain until typical manifestations of yellow fever developed.

*Physical Examination.*—On admission, the patient appears restless with anxious expression; the face is flushed; the conjunctivae are injected; the gums are swollen and bleed easily on pressure. Hemorrhages into the skin are found occasionally (Fig. 2), varying from 0.1 cm. to several centimeters in diameter. They are usually irregular in outline. Infected mosquito bites on the forearms or legs are seen frequently. The mucous membrane of the mouth is congested. Herpes labialis was present only in two cases. The lymphnodes are not

enlarged. The lungs, except in terminal hypostasis or pulmonary edema, are clear. The heart is usually normal. Occasionally, during the height of the disease, a precordial systolic murmur was heard, and rarely premature contractions were noted. The abdomen is usually diffusely tender; the epigastrium and liver edge are exquisitely tender. The liver was not definitely enlarged, except in a few cases. The spleen is not palpable in most cases of frank yellow fever; it was definitely enlarged only in suspected malarial cases. Tenderness on pressure over the kidney region in the flanks is usually marked. The skeletal muscles are ordinarily tender during the entire course of the disease.

During the second period of the disease the patients are usually quiet, relaxed, jaundiced, weak, apparently dried out and very ill.

There is a loss of body weight, averaging about one pound per day during the active course of the disease. The most marked loss of weight recorded was 17¾ pounds in sixteen days. With the onset of convalescence the normal weight is regained promptly.

*Temperature.*—The fever is relatively low, continuous and usually of short duration. After reaching its height on the first day, the temperature remains remarkably constant for three or four days and then gradually drops to normal from the fifth to eighth day. In a few cases observed early a slight remission on the second or third day was noted. The fever usually lasts about a week. In four patients it was normal on the fourth day. In three apparently uncomplicated cases it remained elevated until the eleventh day. When the patient's condition appears gravest the temperature is usually normal or slightly subnormal.

*Pulse.*—The pulse rate is usually relatively slow during the febrile period, in proportion to the fever curve. Early and during the postfebrile period the pulse rate is proportional to the temperature curve. The bradycardia is moderate and relative, rarely absolute. A pulse rate of 50 or less was observed fourteen times and constituted a grave sign. Eight of these fourteen patients died; the others recovered after very severe courses. A terminal rise in the pulse rate is the rule. The pulse is usually full, soft and regular, occasionally dicrotic and rarely intermittent.

*Respiration.*—In the first few days of the disease there is a subjective dyspnea of which the only objective evidence is an occasional deep sighing respiration together with a peculiar whistling expiratory note. Except for this dyspnea, the respiration in the light and moderately severe cases was apparently normal through the entire course of the disease. In the severe cases, those that were evidently uremic, a variety of respiratory abnormalities were encountered. Deep expirations, accompanied by moaning and groaning, were common; air hunger

of maximum intensity, lasting irregularly for hours, or Cheyne-Stokes respiration, typical or variously modified, were common as terminal events.

*Jaundice.*—Jaundice is a constant though variable manifestation in all cases. It is usually proportional to the severity of the disease, inconspicuous in most of the light cases, although sometimes marked as compared to other manifestations, and intense in the severe cases. It appears, as a rule, on the third or fourth day, occasionally as early as the second day. A maximum intensity is reached about the tenth day and continues well into convalescence. Jaundice was still intense in some cases at the time of discharge when the patient was otherwise apparently well. In three light cases it appeared for the first time during convalescence, on the eighth, tenth and fifteenth day, respectively. Fifteen patients were admitted before jaundice had appeared. All patients admitted *in extremis* were intensely icteric.

The pigmentation is first noted in the congested conjunctivae, increasing as the congestion disappears. The skin and mucous surfaces are discolored later. Skin jaundice was sometimes difficult to detect because of the dark complexions of the patients. The blood serum and the urine are often markedly pigmented, out of proportion to the degree of jaundice evident elsewhere, and remain so for a longer time.

The jaundice itself is apparently nontoxic; skin itching does not occur. On only two occasions were patients observed scratching the skin, although attendants were constantly watching for this manifestation. At the end of convalescence intensely jaundiced patients appear to be free from obvious toxic symptoms.

The jaundice is apparently primarily of the dissociated type. The blood serum of all patients definitely pigmented gives a positive, often intense, Gmelin test for bile pigment; only four of ten serums tested gave a weakly positive Pettenkofer test for bile salts on aqueous dialysates.

The urine, always intensely pigmented, uniformly gives an intense Gmelin test for bile pigment, but a negative, or, at most, a faintly positive, Hay or Pettenkofer test for bile salts. In all markedly jaundiced patients the foam of the urine is definitely yellow. Some specimens showed evidence of large amounts of urobilin, although some of the most intensely pigmented urines showed none.

The stools, in a few cases, were distinctly clay colored, but in most cases they were dark brown and contained much blood.

From the clinical and postmortem evidence one must conclude that the degenerated liver of yellow fever is incapable of performing its function; that it not only acts as a barrier to the normal turnover of

pigment in the body, but that it is also incapable of secreting bile salts. The jaundice is, therefore, primarily a hepatic dissociated jaundice, although it is evident from the presence of traces of bile salts in the blood in three of eight cases tested, that there is also some resorption as a result of bile capillary obstruction.

*Blood.*—Blood examination shows little that is characteristic. The red blood cell count is rather high in proportion to the low percentage of hemoglobin, possibly due to the fact that most of the patients had recently left the mountains to reside at the sea level. The average count was within the normal range, although three counts of more than six million and nine of less than four million were obtained. The lowest counts were obtained in patients having uncinariasis.

The average white blood cell count is about normal. A definite leukopenia of less than 4,000 occurred in only nine cases. High counts, from 13,000 to 49,000, were obtained in moribund patients, usually uremic, although it is noteworthy that some comatose patients showed normal white counts. Apparently, there is no rule that can be applied to the light and severe cases in so far as the white blood count is concerned, as both high and low counts were obtained in both groups.

The hemoglobin, as estimated by a Dare instrument, is uniformly low. Estimations between 40 and 60 per cent. were common; more than 90 per cent. was found in three cases, estimations of from 80 to 90 per cent. were obtained in ten cases. One patient with uncinariasis had 28 per cent. hemoglobin. Hemoglobin does not drop proportionally as jaundice progresses. The estimation of the percentage of hemoglobin is, to some extent, rendered inaccurate because of the presence of bile pigment in the intensely yellow blood serum of all severe cases. Higher readings than the actual amount of hemoglobin present would warrant are accordingly obtained. A drop in hemoglobin was noted in a few severe cases as the disease progressed, from 65 to 58 per cent. and from 48 to 28 per cent. On the other hand, the percentage of hemoglobin seemed to increase as the disease progressed in some cases, due, possibly, to the large amount of bile pigment present in the blood plasma early and to dehydration later in the course.

The differential count shows only normal variations. An unexplained eosinophilia of 30 per cent. developed in one case, while under observation. A vacuolar degeneration of the white blood cells was present in thirteen of eighteen blood smears, especially examined for this point and seemed most marked in moribund patients. Blood platelets are always present, apparently in more than the normal number.

The coagulation time of the blood is well within the normal range, averaging from one to three minutes even in patients with continuous

hemorrhage. In only three cases was the coagulation time found to be more than four minutes.

Aestivo-autumnal malarial parasites were found in the blood of five patients, while in a few cases with undoubted coincident malaria they could not be detected.

The washed red blood cells show normal resistance to hypotonic salt solution. Fifteen tests on eight jaundiced patients gave results which were well within the normal range, although there seemed to be a range of hemolysis slightly wider than the normal, for example, hemolysis beginning at 0.40 per cent. sodium chlorid solution and complete at 0.28 per cent. in one case, and a range of 0.42 per cent. to 0.30 per cent. in another case. No satisfactory explanation of this is evident.

*Blood Pressure.*—The blood pressure is uniformly low, systolic 110 or less and diastolic 65 or less, as a rule. Otherwise nothing distinctive was observed. The pulse pressure is not distinctive.

*Hemorrhage.*—Hemorrhage is one of the distinctive manifestations of the yellow fever cases of this series. It was observed clinically in all severe cases which remained under observation long enough for this point to be determined. Thus, hemorrhage, in one form or another, was observed in thirty-four cases; it was absent in seven cases, only one of which was considered severe. Eight patients were not under observation long enough for the determination of this point. Hemorrhage occurs in many forms, and apparently, from almost any tissue. The nasal and gingival mucous membranes and the gastro-intestinal and genito-urinary tracts are the principal sites of hemorrhage. In all of the nine necropsies performed extensive hemorrhages were found, principally into the gastro-intestinal tract, lungs, kidneys, papillary heart muscle, uterus, mesenteric glands, suprarenals and on the subserous surfaces of organs such as the heart, lung, stomach, bowel, liver, gallbladder and kidneys.

Alarming hemorrhages occurred from the gums (Figs. 3 and 4), gastro-intestinal tract, uterus, or urinary tract in sixteen cases, lasting often for days, as in the case of bleeding from the gums, stomach or bowel, or appearing suddenly and intermittently as from the nose or uterus.

Slight epistaxis occurred early in only seven cases, and this fact was elicited only on inquiry. Severe epistaxis occurred later in twelve cases from the fifth to the twelfth day. Bleeding from the gums was noted in twenty-one cases. Blood can be expressed from the gums of most patients at the height of the disease. In nine cases the hemorrhage was alarming, continuing for days. "Black vomit" occurred while under observation in fourteen cases; it was absent in seventeen

of thirty cases observed long enough to determine this point. It had occurred in all of the cases in which a postmortem examination was made. The vomitus is for the most part of coffee-ground appearance; in two cases bright red blood was present.

Hemorrhage into the skin, with areas from one millimeter to several centimeters in diameter, was observed in seven cases. Free bleeding from the surface of the thighs following irritation as a result of prolonged menstrual flow, was alarming and constant in one patient. Uterine hemorrhage occurred in three cases; it was spontaneous and alarming in two cases. Hematuria continuing for days was observed in two patients.

In general, hemorrhage occurs in all severe cases of yellow fever during the second and third weeks. The light cases do not bleed. The administration of horse serum in six cases had no perceptible effect on the bleeding.

Figure 3

Figure 4

Fig. 3—Boy, 11 years of age (Case 32); sixth day of disease. Gums swollen and bleeding; sclerae congested; intense jaundice; recovery.

Fig. 4.—Severe, fatal case (Case 1); male, 23 years of age; fifth day of disease; twenty-four hours before death. Herpes labialis; swollen and bleeding gums and intense jaundice.

It is significant that the hemorrhage does not parallel the jaundice. Hemorrhage is greatest at the height of the disease, while jaundice reaches its maximum after convalescence has begun and persists to a marked degree well into convalescence.

The facts that the coagulability of the blood is normal, that the administration of horse serum is without effect and that the hemorrhage does not parallel the jaundice, seems to indicate that hemorrhage in these cases is due to injury to the vessel walls rather than to some abnormal condition of the blood itself, such as a deficiency of calcium or the presence of bile salts and pigments. These facts seem to indicate that there is a degeneration of blood vessel endothelium proportional to the degree of general parenchymatous degeneration.

*Urine.*—The urine in all cases is very highly colored, from dark yellow to olive green, with yellow foam. The amount passed in one day varied from an average of 700 c.c. to complete anuria, which usually foreshadowed death. Except in moribund cases, the amount of urine is directly proportional to the fluid intake, and can always be increased by increasing the intake even in the presence of persistent vomiting. The intestinal tract is apparently able to absorb fluid, and the kidneys are apparently able to excrete it in spite of intense degeneration.

Albumin appears as a trace on the second or third day, increases rapidly to enormous amounts, 3 or 4 gm. per liter, during the second week, and then decreases gradually and finally disappears entirely during the third or fourth week. The albuminuria reaches its height several days after the termination of fever. During the second and third days casts appear in great quantities, paralleling the albumin. These casts are chiefly of the large granular type. They are thickly matted together in the centrifuged specimen.

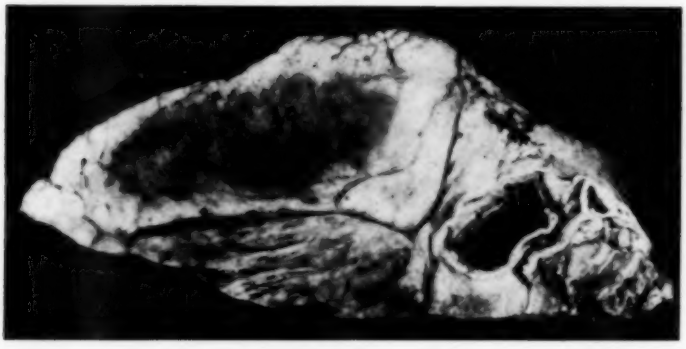

Fig. 5.—Heart, showing superficial, punctate hemorrhages scattered over the surface.

In light cases albumin and casts are constantly present out of proportion to the other manifestations of the disease, a phenomenon which is of value in diagnosis. Red blood cells are present in all urines at the height of the disease. Swollen, round, apparently detached endothelial cells with large nuclei are numerous, apparently paralleling the other manifestations of nephritis, although they often appear earlier and persist later than the intense cylindruria. Bilirubin was always present (Gmelin test); urobilin was frequently demonstrable by Schlessinger's test but appears least intense in the most highly pigmented urines; bile salts were often demonstrated by Hay's and

Pettenkofer's tests, though the reactions were not as marked as were those for bile pigments. In general, the urine gives evidence of an intense nephritis which persists after the fall of temperature and well into convalescence. The disappearance of all signs of nephritis was observed in all patients who recovered and was remarkable because of the apparent intensity of nephritis attained.

*Uremia.*—Uremia is a terminal event in all fatal cases. Of twenty-three patients that showed well marked uremic manifestations, only three recovered; two of the three were wildly delirious on admission. Uremia is usually heralded by a fall in the amount of urine passed in twenty-hours. When complete anuria occurs death usually follows within a few hours. Four patients voided no urine for twenty-hours; two of these recovered.

The following manifestations of uremia were noted: air hunger, a peculiar whistling respiration, precordial distress, headache, backache, persistent vomiting, hiccup and, finally, delirium, Cheyne-Stokes respirations, convulsions and coma.

*Stools.*—Most of the patients harbored intestinal parasites. Ova were found in nine of fourteen stools examined. Uncinaria duodenale were found in two patients, *ascaris lumbricoides* in six patients and *amebae dysenteriae* in two patients. Lumbricoid worms were frequently present in the vomitus or stools during the height of the disease.

## COMPLICATIONS AND SEQUELS

Complications and sequels are uncommon. Parotitis occurred in two cases; phlebitis in one case; acute pain and swelling in the joints, interpreted but not demonstrated as hemorrhage, in three cases. A persistent diffuse bronchitis, interpreted as secondary to hemorrhage into the lung, was present in two cases. Secondary infection was suspected in a few cases, but was demonstrated only once during life. In the nine cases in which a postmortem examination was made there were no findings, such as exudates, endocarditis, pneumonia, etc.

## CONVALESCENCE

Convalescence was rapid in all cases which terminated in recovery, although some patients were weak and many showed varying grades of jaundice at the time of discharge. The latter considered that they were in their usual state of health in spite of the presence of jaundice. No other ill effects of the disease could be detected. Complete restitution from the universally present extreme nephritis apparently occurred in all cases. A few patients were anemic and in poor health as a result of preexisting disease, such as uncinariasis, but as far as the

effects of yellow fever were concerned, complete recovery seemed assured in all of the discharged patients. The rapid and complete recovery of all patients who did not succumb was a constant source of wonder, particularly as contrasted to the incomplete recovery often seen in other familiar severe infectious diseases.

### DIAGNOSIS

The diagnosis was ordinarily not difficult, even as early as the second or third day, and by the end of the fever course it was established beyond question, even in light cases. The chief diagnostic points are enumerated in the order of their importance.

1. The fact that the patient was a foreigner and not a native of Guayaquil or had recently arrived from the interior: The local physicians consider it practically impossible that a child, born in Guayaquil, can grow to maturity without developing yellow fever and, therefore, become immune, or that a susceptible adult can live long in Guayaquil without becoming infected.

2. A low continuous fever course with relative bradycardia: A fever of 40 C. or more speaks against yellow fever.

3. Nausea and vomiting: "Black vomit" is practically diagnostic.

4. Epigastric pain and tenderness, often intense from the beginning.

5. Rapid and progressive development of nephritis, with albumin present as a trace on the second day and increasing to from 1 to 3 gm. per liter on the fourth day.

6. Flushed face, injected conjunctivae, swollen and bleeding gums.

7. The gradual and progressive development of jaundice, apparent in the conjunctivae as early as the third day.

The greatest difficulty in the diagnosis of yellow fever occurred in cases of malaria in which yellow fever developed subsequently. In these cases the high fever course of malaria gave way to the lower but more continuous fever course of yellow fever, associated with a relative bradycardia not previously present. The lower temperature continued for four or five days. After a few days, during the convalescence from the yellow fever, the high temperature of malaria, not always intermittent, recurred (Case 13). The plasmodium was not always demonstrable in the blood, but these cases readily responded to one or two deep injections of quinin. The differentiation of cases of cerebral malaria was difficult and often impossible, except at necropsy. In children, the manifestations of yellow fever were apparently the same as in adults.

PROGNOSIS

The degree of severity of a case of yellow fever could not be foretold at the time of admission. Those patients who were admitted early with much facial congestion, conjunctival injection, swelling of the gums and restless and apprehensive facies and dyspnea, had grave infections which usually were fatal. Tachycardia was always considered of serious import. Uremic manifestations, such as air hunger, restlessness, delirium and coma accompanied by a diminished output of urine decreasing to the point of anuria, were grave signs though not necessarily fatal.

The physical condition of the patient at the time of admission did not seem to have much relation to the progress of the disease. Some patients who had previously been in apparent good health died, while others, debilitated from malaria, uncinariasis and amebic dysentery, recovered.

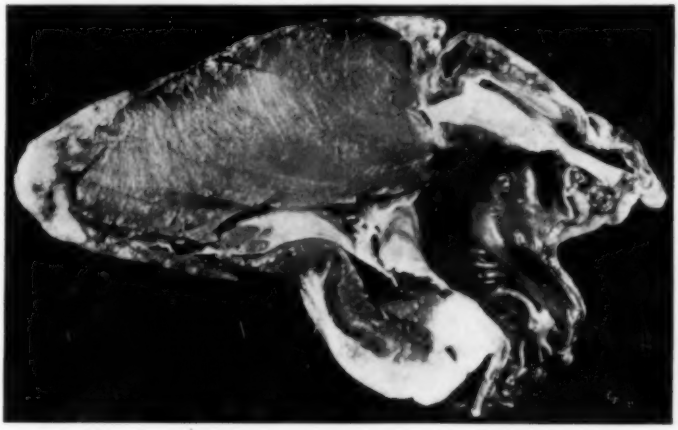

Fig. 6.—Heart, section through interventricular septum, showing myocardial degeneration and punctate hemorrhages at the apex.

Of ten children under 12 years of age, eight had severe attacks and two had light attacks. Six died and four recovered. Although these figures show a high mortality, there seems to be a uniformity of opinion among the local physicians that yellow fever is well borne by children.

MORTALITY

Nineteen of the fifty cases of the series terminated fatally, a mortality rate of 38 per cent. This was considered about the usual death rate from yellow fever in Guayaquil. The mortality rate in all cases

of yellow fever admitted to the lazaretto from January 1, to August 1, 1918, was 44 per cent.

### TREATMENT

The general principles of the treatment of fevers were followed. No specific or special treatment was carried out in the cases studied. Little or no medicine was given and no conclusions can be based on our experience.

Fig. 7.—Heart muscle (magnification 140 diameters), showing degeneration and hemorrhage.

### POSTMORTEM FINDINGS

Nine necropsies[3] were permitted and were held as soon as possible after death. The findings were fairly uniform, consisting, in general, of diffuse degeneration of all parenchymatous structures with numerous hemorrhages in all tissues ranging in size from punctate to widespread areas. The tissues were generally dry and intensely jaundiced, the yellow color apparently increasing after death. Exudative changes were absent in all cases.

3. The microscopic examinations were made by Dr. James P. Simonds, associate professor of pathology in Northwestern University Medical School.

*Heart.*—The heart showed from a few to many punctiform hemorrhages on the surface both of the visceral pericardium and the endocardium, apparently more numerous about the auriculoventricular junction, but present in all cases. Punctiform hemorrhages were found in the papillary muscles in most cases. The myocardium was dry, granular, friable, the interventricular septum showing the greatest change. The valves were not affected. In a few cases there appeared to be some dilatation of the right heart, but never to a marked degree.

Fig. 8.—Lungs, cut sections, showing punctate and confluent hemorrhages.

Microscopically, subpericardial and occasionally intramyocardial hemorrhages were found. The muscle fibers were generally swollen, the striations indistinct and in the most severe cases entirely absent in places. The nuclei of the most affected fibers were absent.

*Lungs.*—The lungs in all cases except one showed from a few to many hemorrhages varying in size from punctate to extensive areas, on the surface and extending deep into the substances. The lungs were dry, fluffy and bloodless in three cases, while pulmonary edema

with much hypostasis, apparently terminal, was present in six cases. The punctate hemorrhages appearing on the surface of the lungs are found to be the bases of deep hemorrhages into the parenchyma, from ½ to 2 cm. in diameter, usually few in number, but sometimes grouped and numerous. A few widespread hemorrhages into the lung tissue were observed. Tuberculous nodules were present in three cases, and old pleural adhesions in six cases. Microscopically, no noteworthy changes were seen.

*Liver.*—The liver was markedly affected in all cases. The size and shape were usually normal; the edge appeared somewhat rounded in some cases. The surface was smooth, from ocher to deep brown in color, with occasional punctiform subperitoneal hemorrhages. In one case there was a widespread subcapsular hemorrhage on the upper

Fig. 9.—Liver, cut section, showing uniform fatty degeneration and absence of hemorrhage.

surface; in one case all the tissues about the hilus, gallbladder and vessels were markedly edematous. The liver was quite firm and cut with resistance in some cases, while it was soft and friable and offered little resistance to the thumb passed through its substance in other cases. The cut surface was dry, smooth and of uniform color, varying from ocher to dark brown in color. Most specimens appeared to be distinctly fatty. It was remarkable that while hemorrhage was observed in all the other parenchymatous tissues, it occurred in the structure of the liver in only one case. The body of the liver, otherwise extensively degenerated, seemed free from hemorrhage. It is possible that the change in the liver parenchyma had passed the hemor-

rhagic stage at the time of necropsy. Subserous hemorrhages of the liver capsule and about the hilus were frequent.

Microscopically, the most pronounced changes were found in the liver. In the patients that died early in the disease the changes consisted of fatty degeneration, located in the intermediate zone of the lobule. In these areas the cell cords were disarranged; some of the cells had lost their nuclei, and there was hemorrhage into the small necrotic foci. The cells elsewhere in the lobule, and especially those immediately surrounding the central veins, showed evidence of fatty

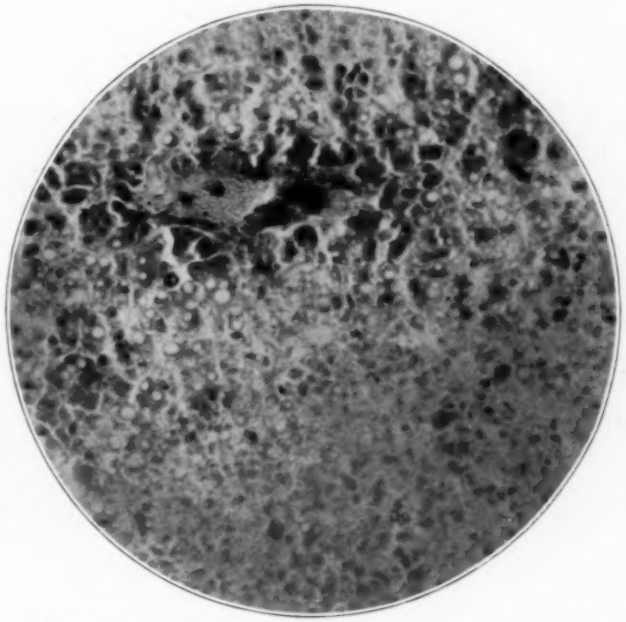

Fig. 10.—Section of liver (magnification 140 diameters), showing extreme fatty degeneration and necrosis of the epithelial cells with hemorrhage into the necrotic areas. The necrosis and hemorrhage are most marked in the mid-zone of the lobule; the cells about the central vein and those of Glisson's capsule are less affected. The cell cords are disrupted.

change and of swelling. In the livers of patients who died later in the disease practically all of the cells of the lobules showed marked fatty degeneration and infiltration; the cell cords were disrupted; there was much necrosis, especially in the intermediate zone; and there was much hemorrhage into the areas of necrosis. Many of the Kupfer cells contained brown pigment. In one instance in which the patient lived for ten days, the longest duration of the series, there was almost

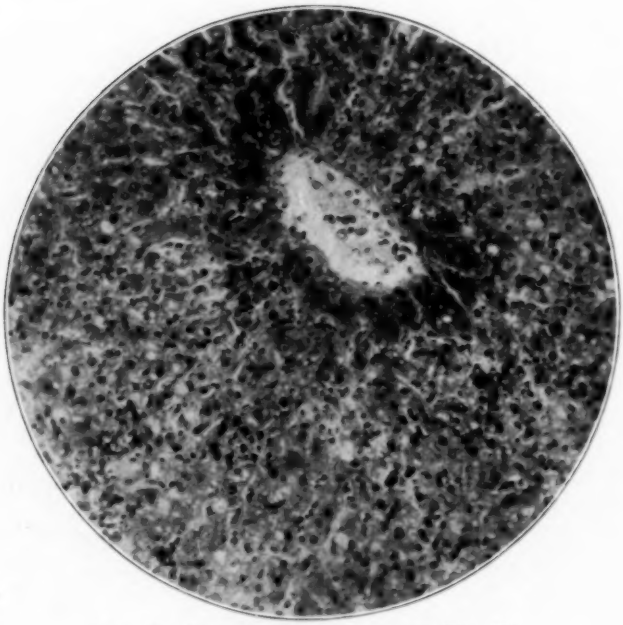

Fig. 11.—Section of liver (compare Fig. 10).

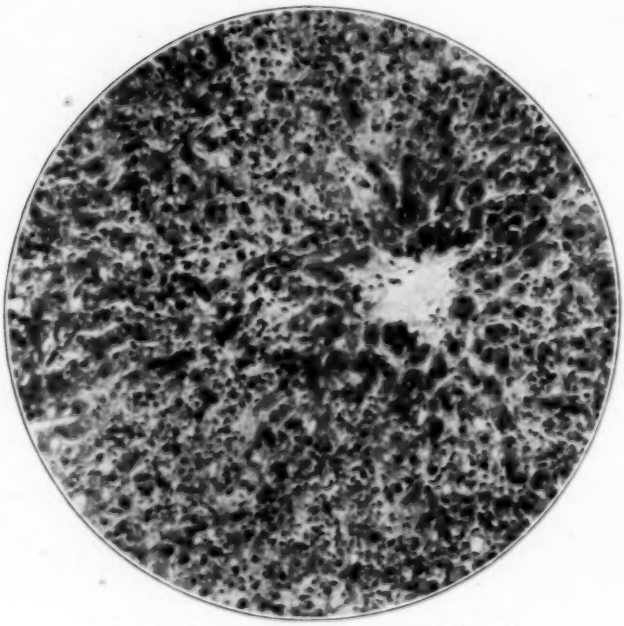

Fig. 12.—Section of liver (compare Fig. 10).

complete necrosis of the hepatic epithelium, only a few poorly staining nuclei being seen at the periphery of the lobules. The structures in the capsule of Glisson preserved their staining qualities.

*Spleen.*—The spleen showed no uniform changes. Some specimens were large, triangular and slate colored, interpreted as of malarial origin; others appeared quite normal. Microscopically, the sinusoids in some cases were dilated but empty. There were no areas of focal necrosis.

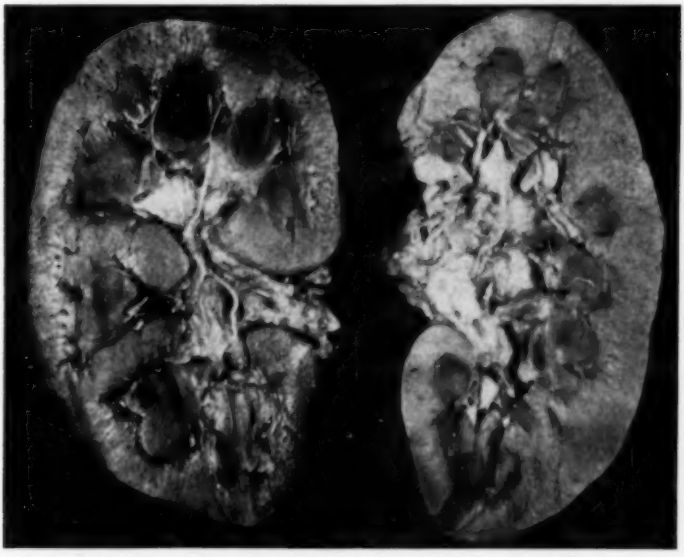

Fig. 13.—Kidneys, cut sections, showing acute parenchymatous changes.

*Pancreas.*—The pancreas appeared to be not grossly affected.

*Kidneys.*—The kidneys were usually enlarged; the capsule stripped readily. The parenchyma was uniformly and diffusely affected, both cortex and medulla appearing swollen in some cases, without any sharp line of demarcation between them. The tubules appeared swollen, some were readily outlined as parallel streaks, some were red and hemorrhagic, others were yellowish in color. The kidneys were all yellow or chocolate colored, hyperemic, sometimes edematous. Seven kidneys showed hemorrhages, punctate to half-dollar size, into the kidney substance, under the capsule or into the perirenal fat. The hemorrhagic areas were usually few in number, although in three specimens they were numerous. In one case there was a large hemorrhage into the pelvis of the kidney.

Microscopically, the most marked changes were found in the epithelium of the convoluted tubules, which showed alterations in structure ranging from cloudy swelling to complete necrosis. In all cases cells could be found which contained vacuoles that probably represented droplets of fat dissolved out in the process of embedding. In general, the amount of necrosis varied with the length of time the patient lived. In those instances in which necrosis was most marked the tubules were filled with a granular mass without any suggestion of cell structure. The glomeruli showed little change other than a moderate hyperemia in some instances. There was occasionally a small amount of exudate in the capsule of Bowman.

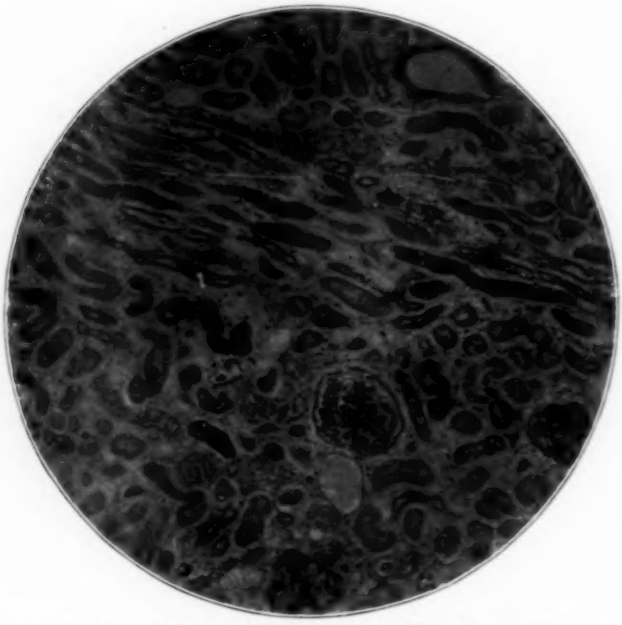

Fig. 14.—Section of kidney. Intense degeneration of the epithelium of the convoluted tubules, completely necrotic in places and containing granular casts at other points. The epithelium of the collecting tubules is less affected. The glomeruli are hyperemic; some show a slight exudate in the space of Bowman's capsule.

*Stomach.*—The stomach showed punctate to extensive hemorrhages into the mucosa, with erosions. Hemorrhages were always more marked at the cardia and lesser curvature than at the pyloric end. "Black vomit" was found in every stomach examined, varying in consistency from a thin "coffee ground" liquid to a sticky, semisolid cho-

colate colored mass which adhered to the mucosa. In two cases there were large subserous hemorrhages near the cardia.

*Intestines.*—The intestines in all cases showed diffuse, punctiform, often confluent hemorrhages into the mucosa. The intestinal content was a semisolid chocolate colored, bloody material. One case showed extensive chronic amebic ulcerations of the sigmoid.

An extensive suprarenal hemorrhage was present in one case, and the mesenteric glands were enlarged and hemorrhagic in two cases. In

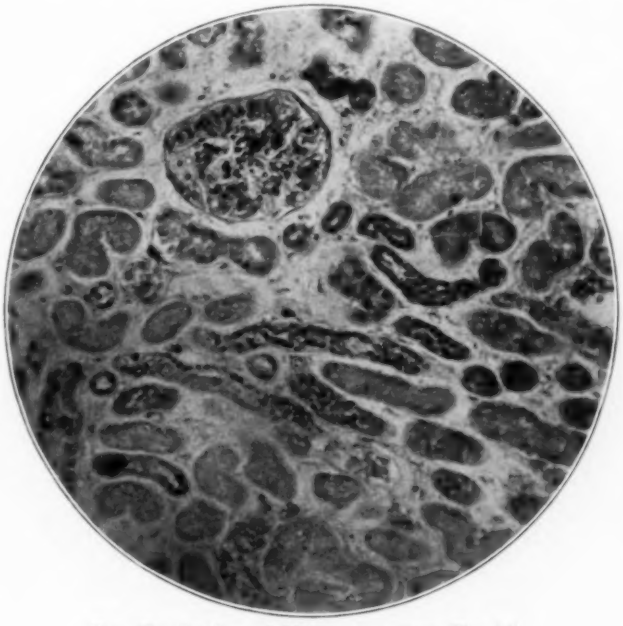

Fig. 15.—Section of kidney (compare Fig. 14).

one case there was extensive hemorrhage on the surface of the urinary bladder, and in another an extensive hemorrhage on the surface of the gallbladder.

## SUMMARY

1. The clinical and pathologic findings are summarized from a study of about seventy cases of yellow fever observed in Guayaquil, Ecuador, during the summer of 1918.

2. Clinically, yellow fever is similar to infectious jaundice. The differences existing between the two diseases appear to be chiefly those of degree. There is more marked jaundice and less hemorrhage in yellow fever than in infectious jaundice.

3. Although hemorrhage is a usual occurrence in all severe cases, yellow fever is not a true hemorrhagic disease. The hemorrhage apparently follows necrosis of parenchymatous tissues and endothelial cells.

4. The jaundice of yellow fever appears to be of a nontoxic dissociated, hepatic (suppression) type.

5. Death appears to be due to uremia. It is usually preceded by anuria. There is an intense degeneration of the epithelium of the convoluted tubules. The glomeruli and collecting tubes remain relatively free from degeneration.

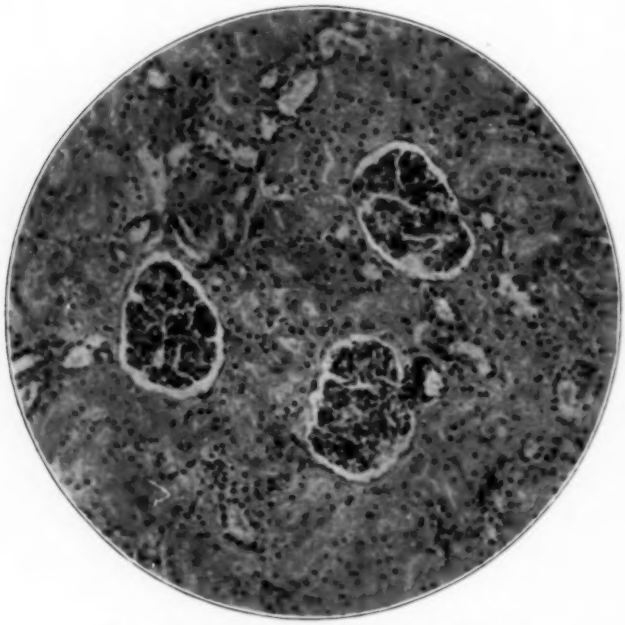

Fig. 16.—Section of kidney (compare Fig. 14).

6. Convalescence in all patients who survive is prompt. The complete restitution of all organs to normal is remarkable. No evidences of impaired liver or kidney function remained, although intense parenchymatous changes must have occurred.

## CASE REPORTS

### Mild Case

Case 12.—Male, soldier, aged 25, native of Cuenca; in Guayaquil three years. Had malaria twice previously.

August 18: Third day of illness. Stomach upset. No vomiting. Fever daily; pain in legs; no headache. Not apparently very ill though prostrated.

Sclerae congested; gums moderately swollen. Glands palpable; inguinal large but not tender. Epigastric tenderness. Lungs, heart, spleen, liver negative. Red blood cells, 5,224,000; white blood cells, 4,800; polymorphonuclears, 66 per cent.; lymphocytes, 22 per cent.; large mononuclears, 12 per cent.; malarial crescents + + +. Albuminuria.

August 19: Urine: albumin +, yellow foam, Gmelin test negative, no casts. Slight jaundice and epigastric tenderness. Feels better.

August 20: Decidedly better; jaundiced; epigastrium tender; liver enlarged. Urine: albumin ½ gm. per liter, no casts; fluid intake 1,500 c.c., output 900 c.c.

August 21: Condition good. Patient comfortable; intensely jaundiced; gums swollen.

August 22: Patient less jaundiced; anemic. Has lost weight. Conjunctivae still injected; gums swollen. Albuminuria. Blood pressure, 102 systolic, 50 diastolic. Convalescent.

August 24: Still jaundiced, feels well. Red blood cells, 5,424,000; white blood cells, 8,600; coagulation time, ½ minute. Discharged. (Fig. 17.)

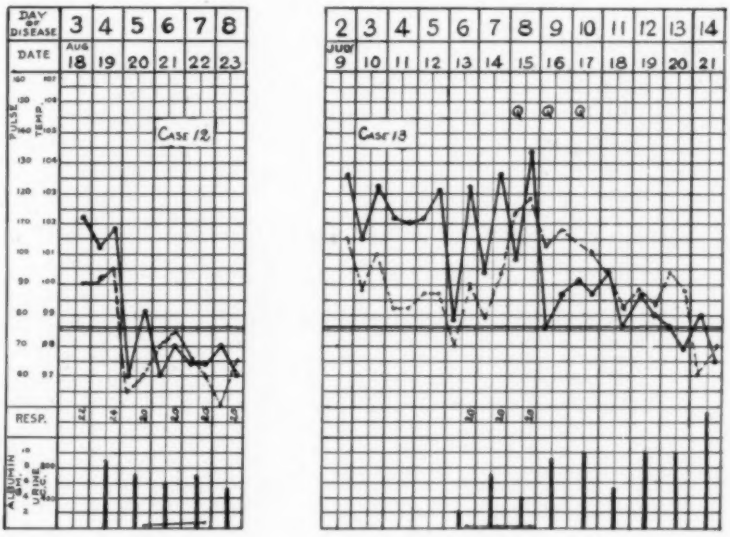


Fig. 17.—Clinical record of two mild cases (Cases 12 and 13) of yellow fever. One of the cases (Case 13) was complicated with a coincident malaria.

### YELLOW FEVER (MILD) WITH COINCIDENT MALARIA

CASE 13.—Male, laborer, aged 18, native of Santa Rosa de Ambato; in Guayaquil fifteen days.

July 9: Onset two days ago with headache, nausea, fever, no chill. Vomited after medicine. Slight epigastric pain; jaundiced.

July 16: Albuminuria on sixth, seventh and eighth days of disease; none on ninth. Physical examination negative except for some enlargement of axillary glands. Patient is recovering from yellow fever complicated by malaria. No parasites were found in the blood, but there was prompt response to two intramuscular injections of 0.5 gm. quinin.

July 18: Feels well; no jaundice. Liver palpable one inch below the costal border; not tender.

July 20: Feels perfectly well. Patient went through a typical yellow fever course but at the end of that time the temperature assumed an intermittent course. After three days of intermittent fever quinin was given for three days and temperature fell to normal. (Fig. 17.)

### Severe Cases

Case 44.—Male, servant, aged 16, native of Cualaceo; in Guyaquil three months. Had malaria in May.

August 9: Ill four days; onset with pain in back, arms and legs; fever; vomited on third and fourth days. No bleeding. Continuous epigastric pain. Stools show ova of trichocephalus. Blood pressure 82 systolic, 56 diastolic. Red blood cells, 3,864,000; white blood cells, 8,000; polymorphonuclears, 54 per cent.; lymphocytes, 32 per cent.; large mononuclears, 12 per cent.; myelocytes, 2 per cent.; no malarial parasites; hemoglobin, 56 per cent.

August 10: Intense jaundice; epigastrium very tender; liver swollen, edge rounded; spleen not palpable. Severe epistaxis.

August 11: Vomited liquid diet. Backache and epigastric tenderness. Condition improved. Intense jaundice; liver small, tender; gums swollen and tender. Examination otherwise negative.

August 12: Still very ill. No change.

August 13: Appears better; jaundice less; gums not swollen; epigastric tenderness less; nausea. Blood pressure 94 systolic, 58 diastolic. Fragility test, 0.42-0.33.

August 15: Improved. Skin dry; no hemorrhages; jaundice nearly disappeared. Physical examination negative. Albumin and casts in urine. Blood culture sterile.

August 16: General improvement but febrile. Jaundice slight; recurrence of epigastric tenderness; albuminuria.

August 17: Marked epigastric tenderness; albuminuria and a moderate number of casts.

August 18: Second rise in temperature. Diffuse râles throughout chest, more on left; apparent diffuse bronchitis. Heart and spleen negative; liver palpable; tender; muscles tender.

August 19: Epigastric tenderness slight. Bronchial râles present throughout chest. Urine: albumin, none; many casts.

August 21: Severe bronchitis, coughs frequently. Jaundice and congestion of sclerae disappeared. Skin covered with sudamina. Heart quick, otherwise negative. Epigastrium tender.

August 23: Lungs show diffuse râles, congestion at base. Many pus cells in sputum, no tubercle bacilli found. Patient has lost weight.

August 26: Red blood cells, 3,232,000; white blood cells, 13,200; polymorphonuclears, 40 per cent.; lymphocytes, 24 per cent.; eosinophils, 30 per cent.; large mononuclears, 6 per cent.; no malarial parasites; coagulation time 1½ minutes; large fat bacillus found in blood smear. No albumin in urine.

August 27: Discharged in good condition.

Comment: This patient had a severe attack of yellow fever. There was a long continued secondary fever with diffuse lung involvement possibly diffuse bronchitis (or punctate hemorrhages?) of unknown origin. Terminal eosinophilia not explained. Recovery. (Fig. 18.)

Case 17.—Male, servant, aged 20, native of Ambato; in Guayaquil two months.

August 17: Onset yesterday; awakened feeling well. At 10 a. m. had general aching of body, then headache, slight fever without chills. Today patient is feverish, eyes congested, gums swollen, not bleeding. Tongue dry, heavily coated. Chest and abdomen negative; slight epigastric tenderness; no muscle tenderness in extremities; no jaundice. Urine: albumin +, no casts. Blood pressure 126 systolic, 58 diastolic. Hemoglobin, 65 per cent.; coagulation time, 1½ minutes; red blood cells, 4,056,000; white blood cells, 7,800; polymorpho-

nuclears, 81 per cent.; lymphocytes, 12 per cent.; large mononuclears, 7 per cent.; malarial parasites, none.

August 18: Patient is feverish, listless, groaning. Eyes congested, gums swollen, tongue moist and coated. Heart broader than normal, soft systolic murmur at apex. Lungs, liver, negative. Slight tenderness in epigastrium, no muscle tenderness. Urine: albumin + +, no casts; many large globular nucleated cells in sediment.

August 19: Urine: albumin + +, casts + + + (granular and epithelial); many large globular cells.

August 20: Seems generally better although fever is high. Complains only of headache and some abdominal pain. Occasionally delirious but lies quiet.

August 21: Urine: albumin + + +, casts + +, very yellow. Patient very ill, delirious with intervals of mental clarity. Pulse irregular, gums bleeding, eyes congested. Heart and lungs negative; epigastric and general abdominal tenderness. Liver enlarged to three fingers below arch.

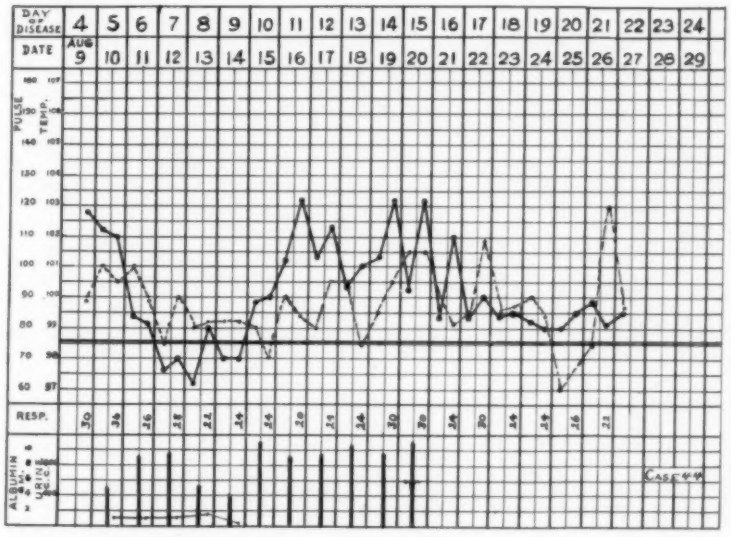


Fig. 18.—Clinical record of a severe case (Case 44) of yellow fever with diffuse lung involvement.

August 22: Oliguria.

August 23: Stools clay colored; urine: albumin + + + +, casts + +, 570 c.c. voided in twenty-four hours. Blood pressure 86 systolic, 58 diastolic. Much bleeding from gums, skin dry, intensely jaundiced, relaxed, emaciated. Glands, lungs, spleen negative. Epigastric tenderness intense, some general abdominal tenderness, no skin hemorrhages.

August 24: Mentally clear, much jaundice, less bleeding from gums.

August 25: White blood cells, 18,200; very weak; jaundice intense; bleeding from mouth; lies quiet, relaxed. Urine contains gross blood in quantity. Epigastric tenderness has disappeared, spleen not palpable.

August 27: Slightly improved, jaundice intense, eyes congested, gums congested but not bleeding. Mucous membranes moist and jaundiced, skin soft and moist, heart and lungs negative, abdomen slightly tender, liver enlarged, spleen

apparently enlarged, not palpable. Blood pressure 110 systolic, 58 diastolic. Hematuria.

August 28: Hematuria intense; 920 c.c. urine voided in twenty-four hours.

August 30: Red blood cells, 5,232,000; white blood cells, 7,400; hemoglobin, 58 per cent.; polymorphonuclears, 58 per cent.; lymphocytes, 26 per cent.; large mononuclears, 18 per cent.; malarial parasites, none. Blood pressure 115 systolic, 62 diastolic; urine: albumin +, casts + + +, red cells +. Patient is recovering. Much muscle tenderness; right elbow very painful on movement, not swollen. Emaciated, jaundiced, congestion from eyes and gums has disappeared, sclerae anemic. Heart, lungs, liver, spleen, negative. Slight epigastric tenderness.

September 3: Patient slowly recovering, very weak, hemorrhages have ceased.

Comment: A severe and prolonged case of yellow fever with intense intoxication and severe hemorrhages. Prolonged convalescence. Recovery. (Fig. 19.)

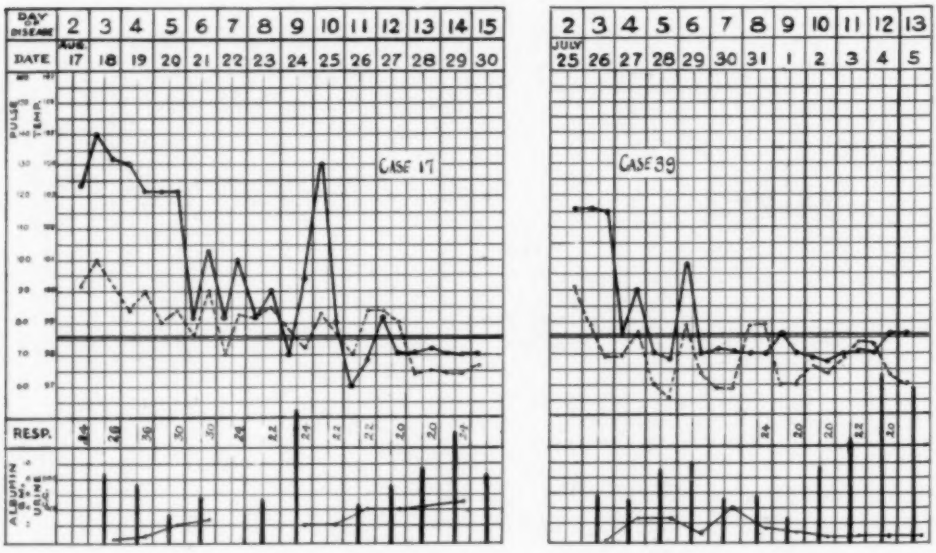


Fig. 19.—Clinical records of two severe cases of yellow fever complicated by intense intoxication and severe hemorrhages (Case 17) and threatened anuria (Case 39).

Case 39.—Male, policeman, aged 23, native of Ambato; in Guayaquil ten months. Had malaria for six days one month previously. Chancre +; buboes four years ago.

July 25: Taken sick two days ago, vomiting daily, headache, fever and chills, pain in abdomen and upper back. One attack of nose bleed—three minutes. Constipated. Patient is well developed, jaundiced; gums swollen, not bleeding. Lungs and heart negative, liver large and tender, spleen large and tender, general adenopathy.

July 26: Blood pressure 102 systolic, 68 diastolic. Urine: albumin + + + +, casts + + + +. White blood cells 4,600. Patient very ill, vomiting, fever, headache, dizzy, weak, sleepless, area of subcutaneous hemorrhage on penis.

July 27: Some improvement, jaundice much more intense. Complains of headache, nausea, vomiting, bleeding gums, thirst, sleeplessness, confusion. Blood pressure 95 systolic, 60 diastolic. Urine: albumin ++++, casts +++.

July 29: Better though still very sick. Daily vomiting, no blood, gums bleeding, intense jaundice and epigastric pain; pulse 66.

August 1: Red blood cells, 4,112,000; white blood cells, 4,200; polymorphonuclears, 63 per cent.; lymphocytes, 33 per cent.; large mononuclears, 4 per cent. General improvement; jaundice more intense; gums bleeding; liver large and tender; no evident skin hemorrhages.

August 3: General improvement; intense jaundice; slight bleeding from gums. Blood pressure 110 systolic, 64 diastolic. Liver palpable, not tender.

August 4: Fragility test, 0.39-0.30. Anuria threatened—220 c.c. in twenty-four hours (improved after forced water intake). Jaundice intense; bleeding stopped from gums. Patient is emaciated and weak, hungry. Red blood cells, 4,032,000; white blood cells, 4,800; no malarial parasites. Allowed to leave hospital on starting convalescence.

Comment: A severe case with hemorrhage and threatened anuria. Patient discharged weak and intensely jaundiced. (Fig. 19.)

Case 7.—Male, soldier, aged 25, native of Guano; in Guayaquil five years.

August 4: Onset August 1, with fever and generalized pain, headache, no chill. Yellow vomitus daily, no bleeding. Red blood cells, 6,896,000; white blood cells, 3,400; polymorphonuclears, 68 per cent.; lymphocytes, 26 per cent.; large mononuclears, 6 per cent.; no malarial parasites found.

August 6: Patient seems very ill, face flushed and jaundiced, eyes congested, sclerae jaundiced. Lungs negative; heart shows occasional extrasystole; liver area small, tender. Blood pressure 84 systolic, 62 diastolic. No ova found in stools.

August 7: Fragility, 0.39-0.33. Urine: albumin, 5 gm. per liter, casts, ++++; water intake 3,850 c.c.; output 650 c.c.

August 10: Patient very ill although apparently recovering from severe attack of yellow fever, jaundice +++; gums swollen and bleeding; fetor ex ore; liver large and tender; spleen not palpable.

August 11: Aching over whole body; weak; relaxed; bleeding from gums; vomiting; no blood; liver tender; skin dry. Urine: albumin, ++++; casts, ++++; yellow.

August 12: Very ill; jaundice intense; epigastric tenderness very marked; heart irregular; gums swollen; bleeding.

August 13: Blood pressure 101 systolic, 70 diastolic. All previous symptoms intense, that is, jaundice, bleeding from gums, pains in upper arms, abdominal tenderness. Fragility, 0.33-0.27.

August 15: Improved but still very sick; listless, depressed; jaundiced; less congestion of eyes; tongue and mucous membranes moist; breath less offensive. Heart slow, regular; liver enlarged; epigastrium tender, lower abdomen not tender; tenderness on deep palpation in extremities. Urine: albumin, ++; casts, ++, intensely yellow. Blood pressure 112 systolic, 56 diastolic.

August 16: Intense jaundice; epigastric tenderness; muscle pain gone, still some backache. Urine: albumin, +; casts, few granular.

August 18: General improvement; intensely jaundiced; spleen edge palpable. Pulse, 58; blood pressure 110 systolic, 68 diastolic.

August 20: Urine: albumin, none; many casts, water intake, 1,500 c.c.; output, 545 c.c. Patient better but weak and relaxed, jaundiced, epigastrium tender, muscles tender on pressure.

August 21: Urine negative. Lungs, heart, negative. Spleen two fingers below arch, general abdominal tenderness, no muscular pain.

August 23: Coagulation time of blood four minutes. Patient convalescent, evident loss of weight, relaxed, jaundice less, abdomen slightly tender.

August 26: Red blood cells, 5,320,000; white blood cells, 3,600; hemoglobin, 63 per cent.; polymorphonuclears, 82 per cent.; lymphocytes, 14 per cent.; large mononuclears, 4 per cent.; no malarial parasites found; coagulation time 1½ minutes. Much scaling of skin. Urine: albumin, +; casts, +.

Aug. 27: Still jaundiced and weak but apparently recovered. Discharged.

Comment: A severe case with prolonged period of intoxication. Recovery complete. (Fig. 20.)

Case 43.—Male, hotel porter, aged 21, native of Cuenca; in Guayaquil four months.

August 14: Sick one day with general body pain, fever, some epigastric tenderness. Blood pressure 110 systolic, 72 diastolic. Red blood cells, 5,840,000; white blood cells, 4,800; hemoglobin, 70 per cent.; polymorphonuclears, 72 per cent.; lymphocytes, 22 per cent.; large mononuclears, 6 per cent.; malarial

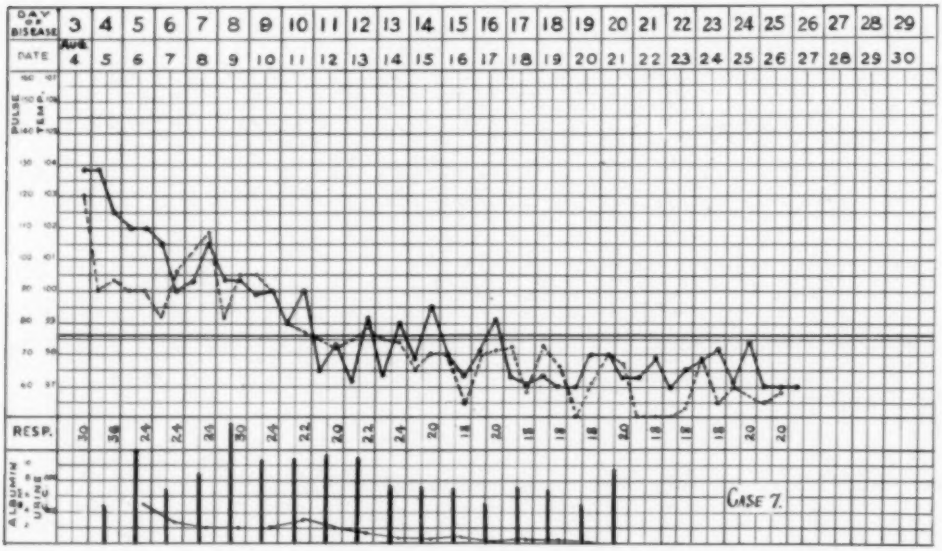


Fig. 20.—Clinical record of a severe case (Case 7) with prolonged period of intoxication.

parasites, none; coagulation time, three minutes. Much congestion of sclerae and diffused redness of conjunctivae, tongue thickly coated in plaques, gums swollen—no bleeding. General slight adenopathy, not tender. Skin hot. Systolic murmur over pulmonic area of heart. Lungs, liver and spleen negative.

August 15: Eyes much congested; no jaundice. Urine: albumin ++, no casts.

August 16: Condition is good; slight jaundice; eyes congested. Systolic murmur over base of left heart; lungs negative; epigastrium tender. Urine: albumin, ++; casts, ++.

August 17: Skin is hot; epigastric tenderness marked. Ascaris ova found in stools. Urine: albumin, +++; casts, ++.

August 19: Urine: albumin, +++; many granular casts. Patient apparently much better; coughing blood; marked epigastric tenderness; lungs and heart negative; intense jaundice; eyes congested.

August 23: Some improvement; no vomiting since yesterday. Gums bleeding and jaundiced. Heart negative; lungs show dulness over right lower posterior lobe; patient coughs. General abdominal tenderness especially in epigastrium; some muscle tenderness. Blood pressure 89 systolic, 58 diastolic.

August 24: Urine: albumin, + + + +; casts, +.

August 26: Urine: albumin, + + +; casts, +.

August 27: Weak, relaxed, intensely jaundiced, hungry. Eyes not congested, swelling of gums slightly diminished—bleeding stopped. No vomiting. Pain in right shoulder which is apparently swollen; muscles not tender but joint painful on motion. Lungs, heart, spleen and liver negative. Left cubital gland enlarged. Muscles tender; abdomen tender. Apparently much better. Blood pressure 98 systolic, 60 diastolic. Urine: albumin, +; casts, +.

August 28: Urine: albumin, +; casts, +.

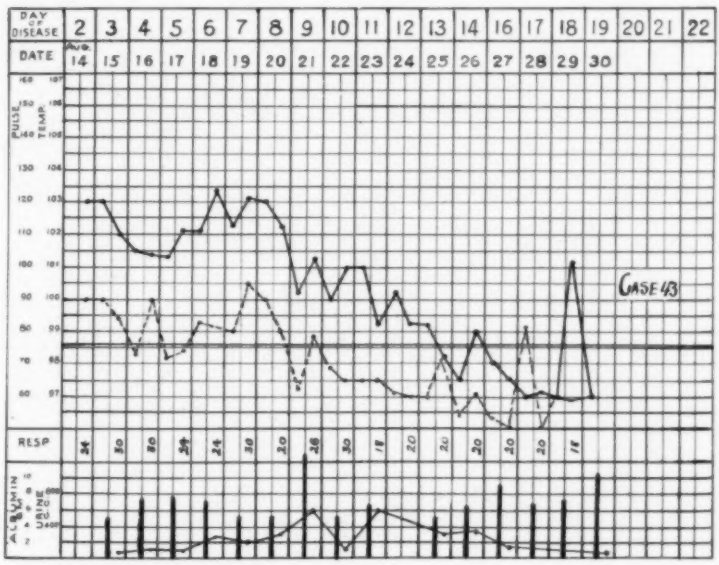


Fig. 21.—Clinical record of a severe case (Case 43) of yellow fever with protracted fever and hemorrhages.

August 30: Red blood cells, 5,232,000; white blood cells, 8,200; hemoglobin, 74 per cent.; polymorphonuclears, 62 per cent.; lymphocytes, 16 per cent.; eosinophils, 2 per cent.; large mononuclears, 20 per cent.; no malarial parasites; coagulation time one minute. Urine: albumin, none; casts, +. Marked improvement. Intense jaundice, gums and mucous membranes somewhat swollen, right shoulder still painful, epigastric tenderness. Findings otherwise normal.

September 7: Discharged apparently well although weak.

Comment: A severe case of yellow fever with protracted fever and hemorrhages (gums, lung, shoulder joint). Recovery. (Fig. 21.)

### Fatal Fulminant Cases

Case 1.—Male, jeweler, aged 23, native of Cajamarca, Peru; in Guayaquil two years and three months. Had malaria in 1916 and five months previous to present illness.

August 23: Ill three days. Severe chill in morning followed by headache, general aching and fever. Nausea and vomiting daily. No hemorrhages. At present patient feels weak with pain in legs.

August 24: Well developed individual; very sick; quiet; eyes extremely congested; sclerae jaundiced; herpes labialis; tongue coated, edges clear; cervical glands are palpable. Heart: systolic impurity over precordia. Lungs, liver and spleen negative. Some epigastric tenderness. Blood pressure 122 systolic, 90 diastolic. Red blood cells, 6,288,000; white blood cells, 4,000; hemoglobin, 96 per cent.; platelets present; malarial parasites not found; polymorphonuclears, 90 per cent.; lymphocytes, 8 per cent.; large mononuclears, 2 per cent. Urine yellow, granular sediment, contained much albumin and casts.

August 25: Mucous membranes everywhere much congested; skin dry, jaundiced; herpes drying; hiccup and vomiting; gums swollen; no hemorrhages. White blood cells, 3,800; polymorphonuclears, 79 per cent.; lymphocytes, 22 per cent. In afternoon patient very ill, mentally confused, delirious.

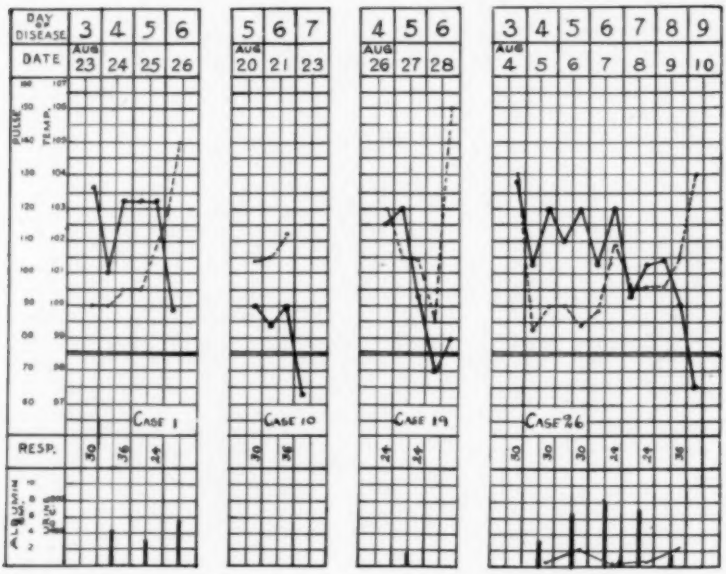


Fig. 22.—Clinical records of four fatal fulminant cases (Cases 1, 10, 19 and 26) of yellow fever.

August 26: Bleeding from gums, much vomiting of black coffee ground material; semiconscious; air hunger; cyanosis; arms cold; pulse feeble; heart rapid (140); lungs negative; bladder distended. Urine contained albumin, +++, many hyaline, epithelial and granular casts. Uremia; coma; death.

Comment: An intensely sick patient on admission, died on sixth day of disease—an overwhelming infection. No necropsy. (Fig. 22.)

CASE 10.—Male, servant, aged 10, native of Yaguachi; in Guayaquil two months. Has had malaria.

August 20: Patient has been ill five days with fever, headache, body pain, nausea and vomiting. Is apparently very sick, stuporous, delirious. Intensely jaundiced, gums swollen and red. Heart, lungs, spleen negative, extreme abdominal tenderness. Red blood cells, 4,392,000; white blood cells, 20,500; hemo-

globin, 74 per cent.; polymorphonuclears, 74 per cent.; lymphocytes, 20 per cent.; eosinophils, 2 per cent.; large mononuclears, 4 per cent.; malarial parasites not found; coagulation time three minutes; blood pressure 98 systolic, 62 diastolic.

August 21: Wildly delirious, crying out in pain, gums swollen, eyes congested. Lungs show many bronchial râles. Heart rapid. Liver negative; spleen not palpable, area of dulness large. Bladder distended, occasional incontinence but no urine procurable. Some epigastric tenderness.

August 22: Comatose, edema of lungs marked, jaundice ++++, gums bleeding, intense air hunger. White blood cells 49,600.

Necropsy, four hours after death: Tissues all yellow and dry. Lungs contain much fluid, hypostasis, many large hemorrhages into lung tissue, tuberculous nodules in right apex. Bronchial glands enlarged, pea size. Heart, no hemorrhages on surface, muscle pale, dilatation of right heart, valves normal. Liver uniformly light yellow, tremendous degeneration. Gallbladder filled, no hemorrhages. Spleen large, slate colored. Kidneys degenerated, hyperemia, no hemorrhages. Suprarenals degenerated, friable. Stomach distended with bloody fluid, subserous hemorrhages and many hemorrhages into mucosa, most extensive at cardia. Mesenteric glands enlarged. (Fig. 22.)

Case 19.—Male, aged 11, native of Guanando; in Guayaquil two months.

August 27: Sick four days, onset with chill and fever, headache; body aches; legs ache. On third day nose bled. Continuous fever. Patient is very ill and toxic, somewhat stuporous, intensely jaundiced, eyes yellow and congested. Heart rapid; lungs, glands, negative; liver enlarged; epigastrium very tender; spleen enlarged one inch below costal arch. Skin hot, dry, no hemorrhages; evidently uremic. Red blood cells, 3,704,000; white blood cells, 5,000; hemoglobin, 48 per cent.; polymorphonuclears, 70 per cent.; lymphocytes, 20 per cent.; large mononuclears, 4 per cent.; myelocytes, 2 per cent.; eosinophils, 2 per cent.; basophils, 2 per cent.; coagulation time, two minutes. Malarial parasites, none. Stools contain ova of trichiuris trichiura and ascaris lumbricoides, no blood. Urine: albumin, +++; no casts; yellow.

August 28: Intensely ill; extreme jaundice; wild delirium, relieved by warm bath. Died.

Comment: This child was admitted in extremis, apparently uremic. Death. No necropsy. (Fig. 22.)

Case 26.—Male, tailor, aged 16, native of Latacunga; in Guayaquil eleven days. Had a fever of unknown cause seven years ago.

August 4: Onset with chill, then fever, headache; vomited once. At present patient is not very sick; there is epigastric pain; abdomen relaxed; liver and spleen negative. Skin shows many subcutaneous erythematous areas, a few hemorrhagic, confluent on lower legs. Red blood cells, 4,928,000; white blod cells, 3,000; polymorphonuclears, 84 per cent.; lymphocytes, 16 per cent.; no malaria.

August 6: Bloody "coffee ground" vomitus.

August 9: Much worse; delirious, jaundiced, gums bleeding, heart rapid. Liver area broad, tender. Red blood cells, 4,816,000; white blood cells, 7,000; hemoglobin, 88 per cent.; polymorphonuclears, 57 per cent.; lymphocytes, 33 per cent.; large mononuclears, 9 per cent.; myelocytes, 1 per cent.; malarial parasites, none. Coagulation time, one-half minute. Blood pressure 109 systolic, 76 diastolic.

August 10: Patient comatose; has incontinence of urine, passing large amounts of intensely yellow urine. Jaundice intense; gums bleeding; pulse, 150; respirations, 50; lungs negative; liver edge extends a hand's breadth below costal arch; spleen enlarged. Death at 2:45 p. m. Urine catheterized after death contained a very large amount of albumin and of bilirubin.

Comment: A severe, fatal case with hemorrhages and uremia. No necropsy. (Fig. 22.)

# PERICARDITIS WITH EFFUSION. AN EXPERIMENTAL STUDY *

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There can scarcely be any better comment on the difficulty in diagnosticating pericarditis with effusion than can be read out of statistics from the postmortem room. Even in institutions where the diagnostic work is admittedly of a high order, the postmortem findings of pericardial exudates entirely unsuspected during life is of not infrequent occurrence. Any one who has been especially interested in the subject must have been struck with the difficulties which are at times encountered in making the diagnosis of such an effusion. Of course, when a well defined friction rub develops in the course of rheumatism, and is followed by a gradual increase in the cardiac silhouette, there can be little difficulty in the diagnosis. On the other hand, in the absence of a pericardial rub, the differentiation between a dilated heart and an effusion may really be very difficult. A considerable number of cases have been reported in which the pericardial sac was aspirated with the expectation of finding fluid, but instead of fluid pure blood came through the needle, in such quantities as to indicate that the heart wall had been punctured. On several occasions I have seen men of distinguished ability do a paracentesis cordis instead of a paracentesis pericardii.

When we examine into the current descriptions of the physical signs in pericarditis, and particularly when we investigate to see on what researches these are based, we meet with a confusion of ideas and statements. While not wishing to discuss the subject from a historical standpoint, a brief statement and criticism of the most important views would seem in place.

One of the oldest views, championed especially by Skoda[1] and his followers,[2] treats of the relations of the heart to the pericardium very

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* Although the casts forming the basis of this paper were exhibited at the 1917 meeting of the American Medical Association, my absence in military service has precluded the earlier publication of the paper.

1. Skoda: Abhandl. ueber Auscultation und Percussion, Wien., 1839.
2. Oppolzer: Vorlesungen ueber die Krankheiten des Herzens, 1867.

NOTE.—In each case the left hand photograph is a picture of the cast of the heart itself; the middle photograph is a cast of the corresponding exudate, and the photograph on the right is a section through the exudate on the dotted line. The chest outline shows the relations of the heart and the exudate as seen from the front.

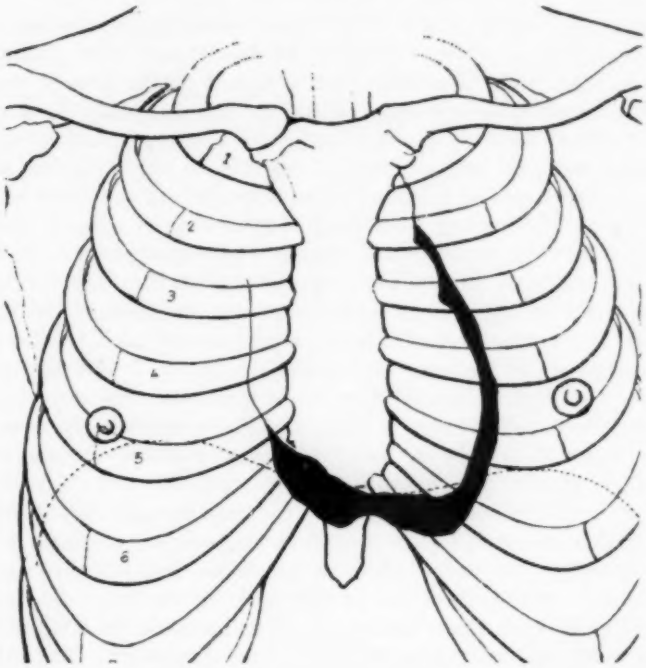


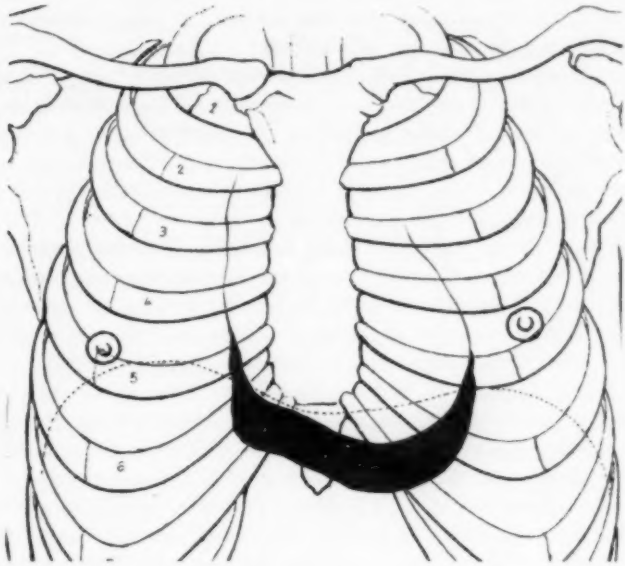
Fig. 1.— Exp. 4; 300 c.c. injected. In addition to the accumulation of fluid on the diaphragmatic surface and around the apex, there is a considerable amount in front of the great vessels at the base. (See note, page 206.)

much in the manner of a vessel of water containing a solid body, the specific gravity of which is greater than that of the water. Inasmuch as the heart, with its contents, has a higher specific gravity than a pericardial effusion, it is manifest that on this theory the heart must needs sink in the fluid to the lowest point of the pericardial sac. It requires, however, only a superficial examination to see that the situation is by no means so simple as this view would lead us to believe. To begin with, the analogy of a solid body sinking in a vessel full of water is far from a correct one, especially with small amounts of fluid. The pericardium is not a vessel with rigid walls, but a tough membrane lying with a large part of its surface in close contact with the heart. It is reflected onto the great vessels at the base, and intimately united with the diaphragm at the central tendon of the latter. It will hold about 100 c.c. of fluid before it begins to be stretched. To surround the heart entirely with a layer of fluid of sufficient depth so that one can talk of the heart "sinking" or "swimming" requires an exudate of considerable size, as can readily be seen from our casts. A second and even more important reason why the heart cannot "sink" freely in the fluid, even when this is present in large amounts, is seen in the attachments of the heart. This fixation, as has been shown by several authors, is quite definite and is produced, on the one hand, by the great vessels at the base, and on the other hand, by the inferior vena cava which anchors the heart firmly to the diaphragm. The axis of fixation extends from the inferior vena cava below, to a point a little to the left of the median line above, which may be regarded as the point of application of the traction of the great vessels. It is plain, therefore, that the only extensive movement of the heart which can occur in pericardial effusion, is of the apical portion.

Quite the opposite of this view is held by Schaposchnikoff[3] and his followers. After a series of experiments, using fluid injections, this author came to the conclusion that the heart swims in the fluid and believes that it is held in this position by the elastic traction of the great vessels. This view is strongly supported, he thinks, by the fact that even with large exudates a loud friction rub may be heard over the entire sternum, and at necropsy the heart may be found in close contact with the sternum. Furthermore, numerous operations on purulent effusions have shown that when an incision is made through the chest wall, the heart itself presents in the wound, and that the purulent exudate can only be reached by pushing the heart out of the way. A case of this sort was reported by me[4] and the patient was operated

3. Schaposchnikoff, B.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **2**:86, 1897. Rev. de Méd. **2**:789, 1905.

4. Med. Clin. **2**:907 (March) 1917.



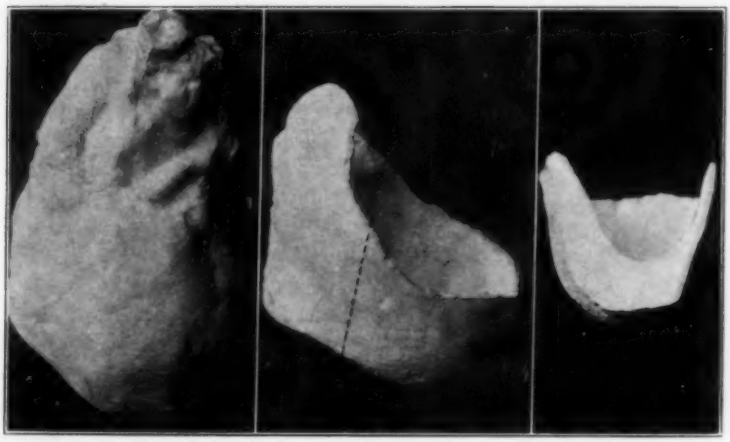



**Fig. 2.—Exp. 18; 240 c.c. injected. A typical small sized exudate is present, confined almost entirely to the diaphragmatic surface.** (See note on page 206.)

on by Dr. Kellogg Speed. The heart was in close contact with the chest wall, and no pus could be obtained until it was pushed back out of the way and the drainage tube inserted.

Curschmann,[5] writing still more recently, holds a view at variance with those of the other observers mentioned. This author holds that the more important factor governing the distribution of the fluid, is the small amount of space which normally exists betweeen heart and sternum in front and the vertebral column behind. He holds that there is very little room for the heart either to "sink" or "swim." The fluid poured out follows the line of least resistance, and not being able to expand anteriorly and posteriorly in the median line, must, of necessity, spread out laterally toward the pleural cavities, or upward and downward in the direction of the great vessels above and the diaphragm below. This author supports his contention by a few cross-sections.

Rotch, of Boston, in 1878 investigated the behavior of the fluid by injecting cacao butter into cadavers and determining by percussion the point of first appearance of the fluid. The subjects had been previously tracheotomized and the lungs inflated until they corresponded in size with the outlines given by Luschka. The most serious objection to Rotch's results is found in that of the sixteen cadavers used—twelve were those of young infants—and that the method is highly subjective. Rotch's results, however, have been quoted widely, and his main contention that a dullness in the fifth intercostal space on the right side is the first sign of a pericardial exudate, has been accepted by many writers.[6] Ebstein[7] in particular, whose attention was called to this sign by reading Rotch's article,[8] expresses essentially the same thought in another way. The angle between the right heart and the liver, the so-called cardiohepatic angle, is normally acute, and he believes that the rounding of this angle is the first clinical expression of a pericardial exudate, and supports this by many illustrative clinical cases. Inasmuch as these findings were all obtained by percussion only, his results lie open to the criticism of subjectivity. Many experienced clinicians have failed to find either the dullness in the fifth right interspace or the rounding of the cardiohepatic angle in proven cases of pericardial effusion.

It is evident that all of these theories cannot be, without modification, reconciled with each other, and with the idea of attempting to bring some order out of the chaos, the experimental work in this research was undertaken.

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5. Curschmann, H.: Die Deutsche Klinik am Eingang des Zwanzigsten Jahrhunderts **4**:401, 1905.

6. Aporti u. Figaroli: Zentralbl. f. inn. Med. **21**:737, 1900.

7. Ebstein: Ueber die Diagnose beginnender Fluessigkeitsansammlungen im Herzbeutel, Virchows Arch. f. path. Anat. **130**:418.

8. Rotch: Boston M. & S. J. Sept. 26, 1878.

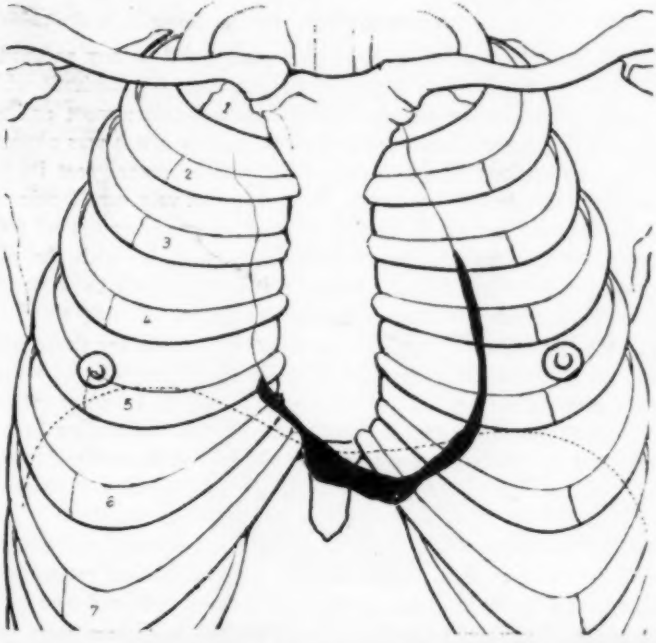


**Fig. 3.—Exp. 26; 175 c.c. injected. The fluid is almost entirely limited to the diaphragmatic surface and covering the border of the right ventricle.** (See note on page 206.)

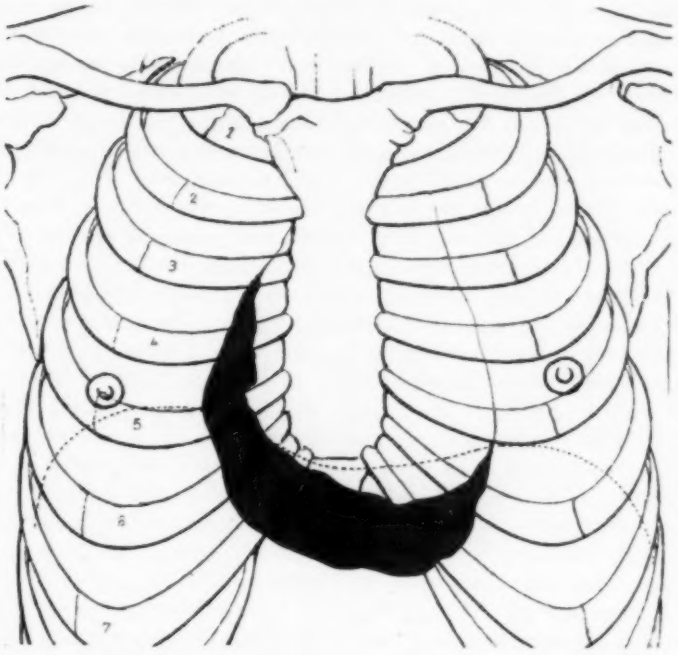
## EXPERIMENTAL WORK

*Methods Employed.*—The most important point in any method is that it shall possess a high degree of objectivity. All methods which depend on clinical observations during life lack this almost entirely, and very little progress has been made with these. Much was expected from the applications of the roentgen ray, but however great its usefulness as a diagnostic accessory, it is of relatively small scientific value in this connection, in that it is open to grave errors of interpretation. When used in the ordinary way, namely, with the plate either on the front or back of the chest, it fails entirely to show fluid accumulations either in front or behind the heart.

The most satisfactory methods for experimentation are those which depend on injecting fluids into fresh cadavers. A number of authors have done this after removal of the sternum, which, I believe, entirely invalidates the work, in that it permits the fluid to accumulate in front of the heart by removing the principal obstacle to its accumulation at that point. A far better plan is to make the injection through the central tendon of the diaphragm, since this can be done without materially disturbing the abdominal relations. I selected for the position of the cadaver that most generally used in clinical examination, such as would be represented by the patient being propped on a pillow at an angle of about 15 degrees. Some of our injections were made with the body at an angle of 120 degrees with the thighs, i. e., in the orthopnea position.

After a great deal of preliminary experimentation, I settled on the following technic, which after the requisite manual dexterity had been acquired, proved to be very satisfactory. A small incision was made in the costoxiphoid angle, through which, guided by a finger, a long specially designed trocar was passed. This was made of tempered steel with a sharp stilet provided with a ball on the outside, from three-eighths to one half inch from the point. The purpose of this ball was to prevent penetration to too great a distance. To make the injection, the trocar was thrust obliquely through the central tendon of the diaphragm, the stilet was then withdrawn and a large brass syringe attached to the needle by a screw thread. The syringe I used held 300 c.c. and was provided with a screw arrangement by which the plunger could be depressed slowly and evenly.

As an injection fluid I settled on a mixture of gelatin and agar-agar made up to the proper specific gravity by the addition of salt. Such a solution, when warm, is perfectly fluid, and under our conditions of experiment, required from one-half hour to one hour to harden sufficiently so as not to be influenced by change of position. To make sure that coagulation would be thorough, we allowed from



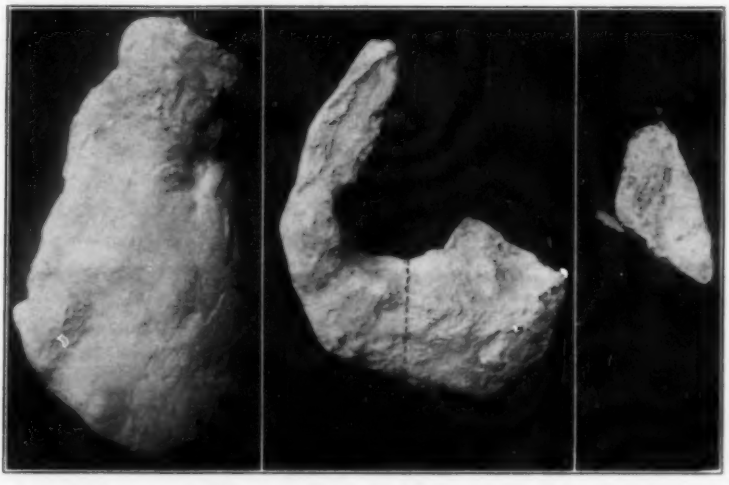



Fig. 4.—Exp. 29; 225 c.c. injected. The larger portion of fluid is on the diaphragmatic surface, pushing down the liver markedly. A thin tongue of fluid runs along the right margin of the heart. (See note on page 206.)

twelve to twenty-four hours to elapse before making the necropsy. All the information which could be elicited by percussion was obtained as the injections progressed. In each case accurate measurements were taken of the thorax circumference and of the distance between the posterior surface of the sternum and the anterior surface of the vertebral column. At the necropsy the fenestrum was carefully removed, and the exact positions of the heart and exudate were measured, the general outline of the heart and pericardium studied, and then the entire pericardial sac and great vessels were removed in toto. The exudate was sufficiently hard so that it could be handled without fear of breaking. It was immediately taken to the laboratory, placed in a low temperature icebox, and thoroughly frozen. The hearts were then turned over to Mr. Hammer, the modeler of the University of Illinois, whose skill needs no commendation. A cast was made of the heart and exudate together. The exudate was then removed from the heart while the latter was still thoroughly frozen, and a cast and model made of the heart itself. The model of the heart was then placed in the mold first made, and the intervening space filled with a plastic mixture, so that an exact model of the exudate was made. In this manner we finally obtained in each case an exact reproduction of the heart, a similar exact reproduction of the exudate, and lastly, a reproduction of the two together. A very important point relates to the size of the exudate. Most authors have contented themselves with injecting fluids, measuring only the amount as it went in, and assuming that it all remained in the pericardial sac. We did this in the beginning, but found the method grossly inaccurate, since as the injections became larger and the intrapericardial pressure higher, the pericardium would be stripped off from the great vessels posteriorly and large amounts of it would escape into the mediastinal and pleural cavities. We lost a large number of experiments in this way, and even in perfectly fresh cadavers, we have not succeeded in introducing larger amounts than 655 c.c. without producing a rupture of the pericardium, or what is more commonly the case, stripping it off the great vessels posteriorly. The exudates were measured entirely by the method of displacement, which gives, of course, absolutely accurate results.

The casts were then photographed in the studio of a commercial photographer with a large camera which was arranged vertically. The casts were placed in their proper position on the floor of the platform, using a long focus lens so that the distance was sufficiently great to prevent appreciable distortion. All of the casts were photographed at one sitting, the camera left set up, the casts were than sawn through and the cut sections brought back and photographed under precisely the same conditions.

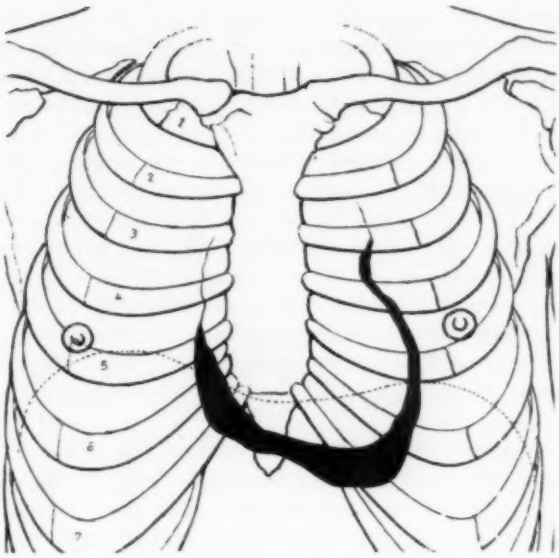


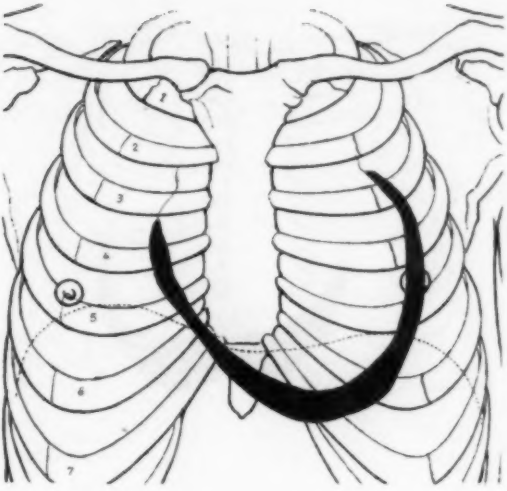
Fig. 5.—Exp. 32; 300 c.c. injected. This shows the greater part of the accumulation of fluid around the apex and diaphragmatic surface. (See note on page 206.)

In order to be able to show accurately the outlines of the hearts and exudates on a chest outline of exactly the same relative size, the following method was adopted: First, I determined the exact amount of reduction of the photograph by comparing the size of the cast with the size of the corresponding print. From the measurements taken of the cadavers an average was struck, and all that it was necessary to do was to obtain a chest outline bearing exactly the same proportion to this average measurement as the photographs of the casts did to the casts themselves. A chest outline was then made to this exact scale. By means of tracing paper, the outlines of the heart and exudate were obtained from the photographs and these placed in position on the chest outline. The accuracy of this was insured by always leaving a considerable length of the great vessels at the base so that there could be no question as to the precise position. In addition to this, the data obtained by the measurements taken at the necropsy were at hand. For invaluable assistance in this work I am indebted to Mr. Thomas Jones, the artist of the anatomic department of the University of Illinois.

In this way thirty-three cases were studied, and I believe that the method possesses advantages over previously used methods in that a great degree of objectivity was attained. The casts are substantial and can be examined and measured in every conceivable way. Particularly, do they show the relations of depth in a way impossible by means of the roentgen ray. My experiences lead me to believe that far reaching conclusions drawn from percussion findings, after the injection of varying amounts of fluid, are apt to be highly fallacious. It is self-evident that percussion cannot possibly give any idea of depth, and affords but a very imperfect idea, if indeed any, of fluid which accumulates between the heart and diaphragm, or in any position where the flatness of the fluid is not in contrast with the resonance of the lung.

*Results Obtained.*—The cases have been divided quite arbitrarily into two groups. The first group includes all those cases in which the exudate measured 350 c.c. or less; the second group included those cases in which the exudate measured between 350 and 655 c.c., the latter being the largest injection. In spite of a large number of injections with larger amounts of fluid, it was invariably found that there had been a small rupture of the pericardial sac, and that much of the fluid had escaped. This is in accordance with the experience of most authors who have made carefully controlled injections.

These two groups will be referred to as the small exudates and the medium sized exudates, respectively. Turning to the first of these, the small exudates (Experiments 4, 18, 26, 29, 32; Figs. 1, 2, 3, 4 and



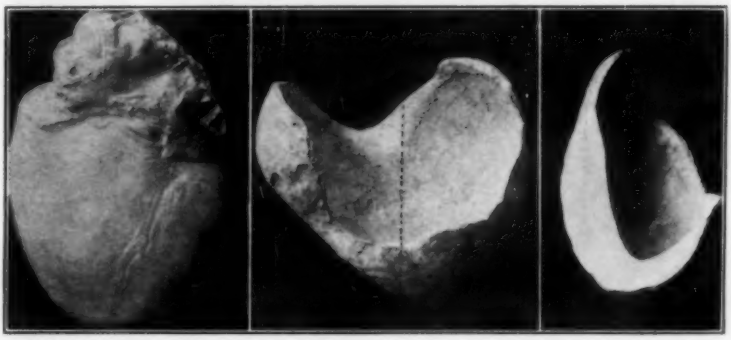
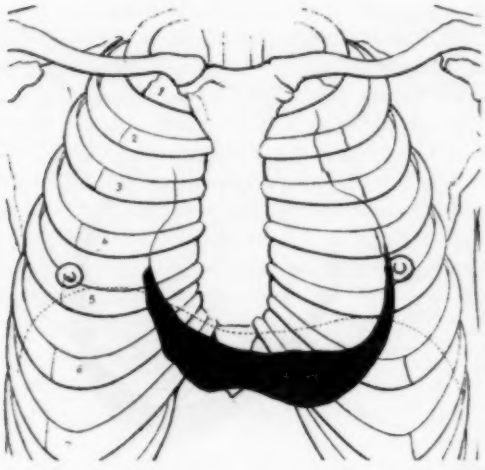



**Fig. 6.—Exp. 1; 460 c.c. injected. Weight of heart 530 gm. The fluid is almost entirely confined to the diaphragmatic surface. The front of the heart is uncovered. This figure illustrates well the point that with large hearts the fluid does not collect in front.** (See note on page 206.)



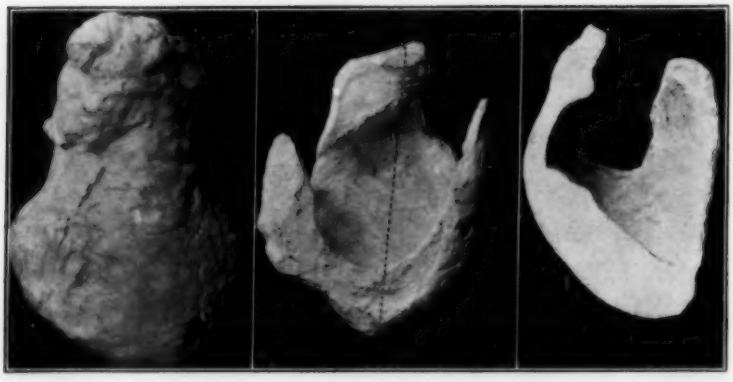
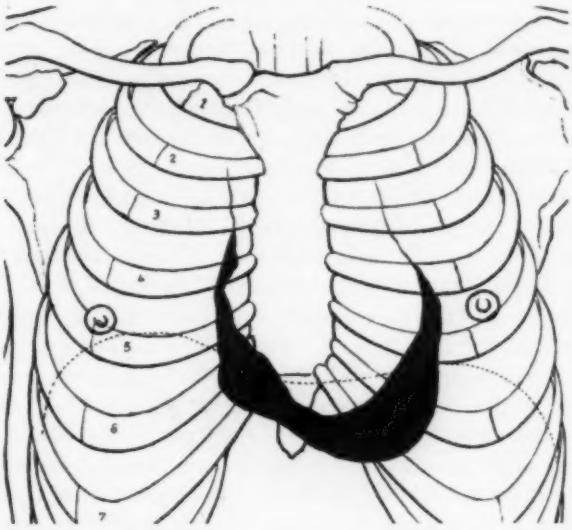


Fig. 7.—Exp. 12; 475 c.c. injected. The heart was very large, weight 550 gm. In spite of the large exudate, the entire anterior surface of the heart remained uncovered. (See note on page 206.)



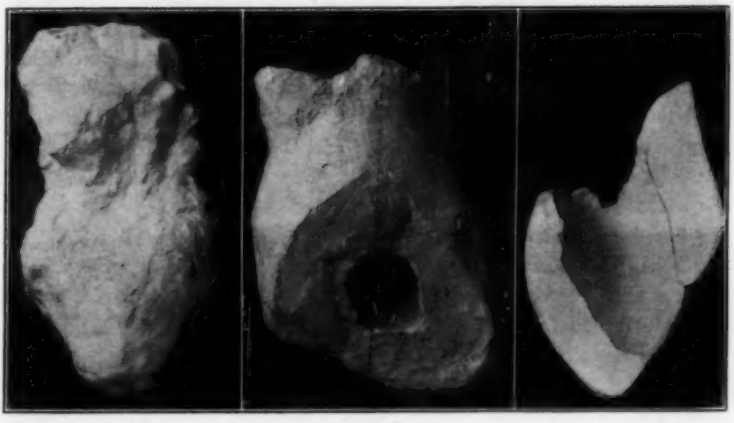



**Fig. 8.—Exp. 16; 425 c.c. injected. The front of the heart is not covered by fluid, which is found in about equal amounts on the diaphragmatic surface and in front of the great vessels.** (See note on page 206.)

5), let us see where the exudate first collected. It is impossible, for lack of space, to reproduce all the photographs. The ones shown are selected as being typical. It requires but very slight study of the photographs and their cross sections to see that in every instance the major portion of the exudate collected in the angle formed by the anterior chest wall and the heart, and to even a larger degree between the right ventricle and the diaphragm, pushing down the latter. In every instance the apex was covered with at least as great a thickness of fluid as the remainder of the diaphragmatic surface. It should be noted that the position of the cadaver makes but little, if any, difference, since in experiments 26, 29 and 32 (Figs. 3, 4 and 5) the cadavers were injected in the upright position; the others were injected in the normal recumbent position.

A careful inspection will show that the liver was materially depressed in practically every case, especially the left lobe, as it presents in the chrondroxiphoid angle. On performing the necropsies the most striking thing noted was *this pushing down of the diaphragm, and with it the left lobe of the liver*. This depression of the left lobe of the liver is more in the nature of a rotation downward than a pushing down of the liver en masse.

A careful inspection of the angle formed by the pericardial exudate and the liver, shows that *in not a single case was this angle obtuse, nor were we able in a single case to demonstrate to our satisfaction a sufficiently marked dullness in the fifth right interspace to be of diagnostic value*. On the other hand, in spite of the fact that in several of the cases the exudates covered the great vessels with a fairly thick layer (as in Experiments 4 and 16; Figs. 1 and 8) we were not always able to determine this with certainty before making the postmortem. The depth at which the great vessels lie, and the readiness with which the exudate in this position may be covered by the lungs, is probably the explanation.

Turning now to the group of medium-sized exudates (Experiments 1, 12, 16, 19, 25, 27 and 28; Figs. 6 to 12) the heart is found relatively more evenly surrounded, and as the exudates grow larger in amount, the anterior surface becomes more frequently covered. In this connection it is necessary to call attention to the fact that in all work on the cadaver, inasmuch as there is no pressure due to the blood in the heart and great vessels, these structures collapse under a much smaller pressure than they would in the living subject, and in so doing become flattened out laterally and, possibly to a very slight extent, longitudinally. This is quite plainly shown in a number of the cuts, giving the appearance of the heart being relatively too large. Intravitam, the

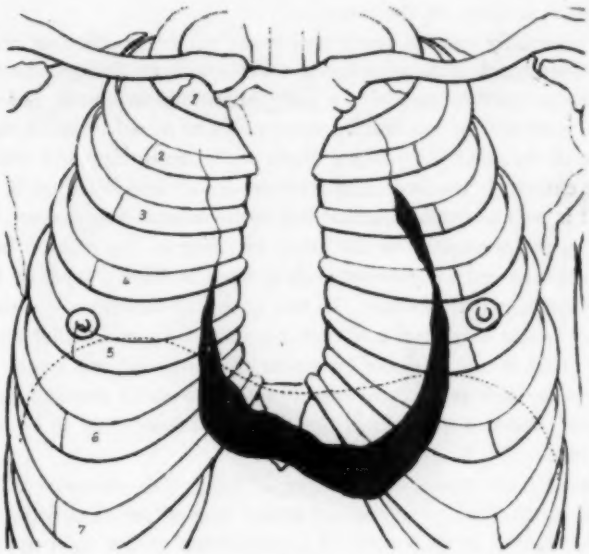


**Fig. 9.—Exp. 19; 435 c.c. injected. The fluid is largely confined to the diaphragmatic area. Note that a large part of the front of the heart is not covered by fluid. Only a small amount of fluid covers the great vessels.** (See note, page 206.)

heart would collapse much less readily, and fluid would less readily accumulate in front of the heart.

An especially careful study was made of the position of the apex beat and we reached the conclusion that there is no change whatever in its position, except, possibly, a very slight displacement downward. This is, however, of too small an extent to be of any clinical moment. In some of the cases the pushing down of the diaphragm and with it the liver, is extremely marked (Experiments 16, 25 and 28; Figs. 8, 10 and 12). It is well to emphasize that this is the outstanding feature, as disclosed by the necropsies in the great majority of the cases. In all of these cases the apex is covered with at least as thick a layer of fluid as is the diaphragmatic surface. In this group of medium sized exudates one may repeat word for word what was said of the smaller exudates, namely, *that in not a single case was the cardiohepatic angle obtuse, nor were we able in a single case to demonstrate to our satisfaction a sufficiently marked dullness in the fifth right interspace to be of diagnostic value.*

One of these cases, Experiment 27 (Fig. 11), occupies an unique position, in that it came from an actual case of pericarditis with effusion, developing in the course of a pneumonia of the right upper lobe. The patient died suddenly and rather unexpectedly, and within a few minutes after death we aspirated through the diaphragm in the usual way and withdrew all the fluid we could obtain, namely, 270 c.c., and immediately injected exactly the same amount of agar solution. It may be noted that the total amount of the exudate as determined by the measurement of the cast was 405 c.c., indicating the difficulty of removing all the fluid. This case is an extraordinarily instructive one, in that the pressure conditions were precisely the same as during life. An inspection of the great veins and auricles especially shows them to be flattened out, and this must have been their condition in the last moments of life. In the light of the work of François Franck[9] and Starling,[10] one cannot help but believe that death in this case was actually the result of excessive pressure, and that had the fluid been aspirated, the pressure factor at least would have been removed. In this particular case a thin layer of fluid covered the heart in front, and extended far up onto the great vessels. I examined the patient about one half hour before death and dictated the following note on the heart: "Apex indistinct; dullness extends outside the midclavicular line in the fifth interspace, and upward along the great vessels on the left edge

9. Franck, François: Recherches, etc., Gaz. hebd. de méd. **29**: 1877.
10. Starling: Some Points in the Pathology of Heart Disease, Lancet **1**:569, 1897.

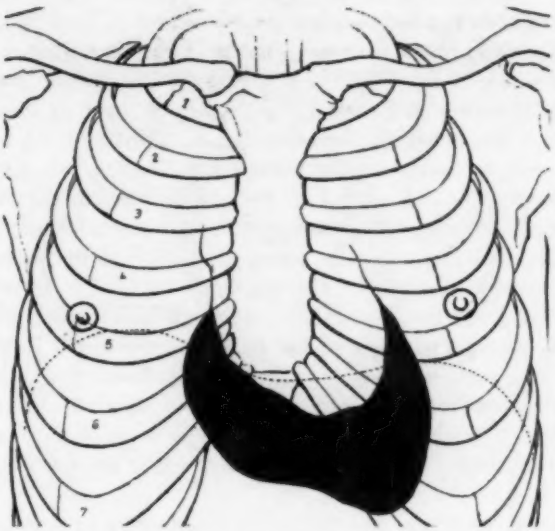
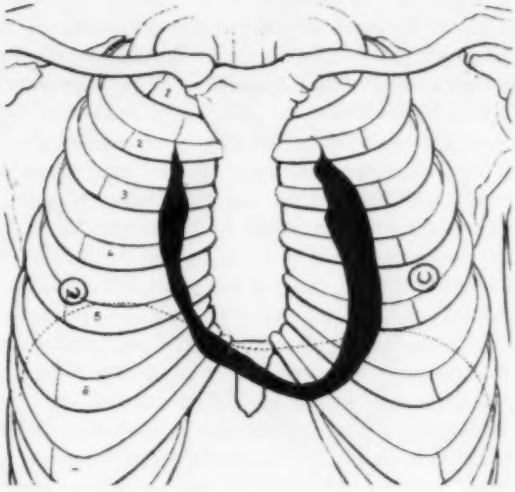


Fig. 10.—Exp. 25; 605 c.c. injected. The striking feature of this experiment is the great displacement of the diaphragm downward. A moderately thick layer of fluid covers the front of the heart and the great vessels. (See note, page 206.)

of the sternum. Right border obscured by the lung dullness. Loud to and fro friction rub over the anterior surface of the heart. Liver dullness extends two inches below the costal arch." It should be noted that this position of the liver was about an inch below what it had been on admission. A study of the photographs and section showed the heart to be surrounded with a fairly uniform layer of fluid, which, however, is somewhat thicker along the left border of the heart, and extends well up over the great vessels at the base. This fact we had been able to make out clinically. Because of the consolidation in the right lung, we could not determine with accuracy what the condition was at the cardiohepatic angle, but an inspection of the section shows that the amount of exudate there was much too small to be determined by percussion, and that the cardiohepatic angle was certainly not obtuse. I wish to lay especial stress on the pushing down of the liver, since it was on this sign, and on the retrosternal dullness that I based my diagnosis of an effusion. It should be noted especially *that despite a layer of fluid, perhaps one quarter of an inch thick in front of the heart, a pericardial friction rub over this entire area could be heard plainly*.

It may be said then, that the principal difference between small and medium sized exudates is that in the latter, in addition to the pushing down of the liver, the heart is more evenly surrounded by fluid. It is especially to be noted that the great vessels at the base are covered with a rather thick layer of fluid in the larger effusions of this group. This can be seen on almost any of the sections cut longitudinally. In most of the cases in which the great vessels were covered by a thick layer of fluid, this could be made out by percussion, but not in all of them, so that while this percussion dullness is to be regarded as a valuable sign when present, it cannot always be made out.

From the standpoint of the persistence of the pericardial rub, it is desirable to note in just what cases the heart remained in actual contact with the chest wall. This was the case in fourteen of the thirty-three cases. In these fourteen cases, exudates of less than 400 c.c. were found in seven, and exudates larger than this were found in the remaining seven. In these fourteen cases, therefore, it is perfectly certain that a pericardial friction rub would have been heard despite the fluid, and recalling the clinical case above enumerated, where a loud friction rub was heard over the entire heart a few minutes before death, although the necropsy disclosed a quarter of an inch of fluid between the heart and the chest wall, it is highly probable that a much larger number would have shown a friction rub despite a fair sized effusion.



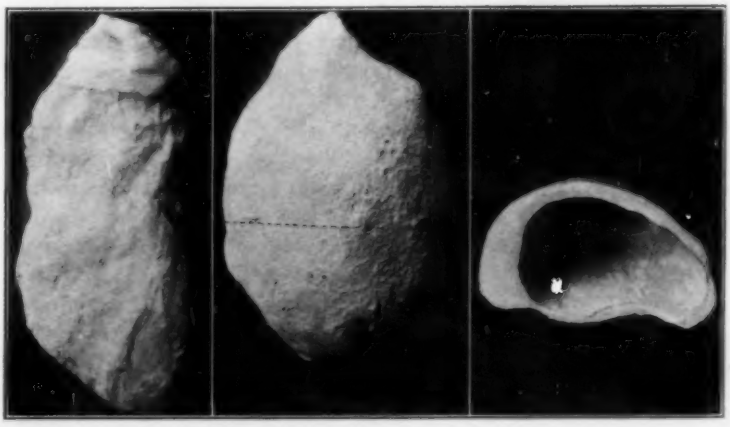


**Fig. 11.—Exp. 27; 405 c.c. injected. This was an actual case of pericarditis. The fluid was drawn off immediately after death and replaced by the same amount of agar solution. In this case the exudate surrounds the heart quite uniformly, a little more along the left border. The great vessels are covered by a fairly thick layer of fluid.** **(See note, page 206.)**

*Relation of Size of Heart and Depth of Thorax to Shape of Effusion.*—It would not be profitable to give all of the numerous measurements taken as to depth of thorax, circumference of thorax, size and weight of heart, etc. Suffice it to say that I have not been able to make out any simple relationship, capable of being expressed in figures, as to the factors which cause the exudate to spare the front of the heart. Despite my inability to express this numerically, a careful inspection of the cadavers at necropsy showed that whenever the size of the heart was sufficient to fill out very fully the anteroposterior diameter of the thorax, there would be no accumulation in front of the heart. Experiments 1 and 19 (Figs. 6 and 9) illustrate this point, Experiment 12 (Fig. 7) is a striking example of it. In this individual the heart was very large, weighing 550 gm., and yet the entire front of the heart was bare of exudate, although this contained the largest exudate of the fourteen mentioned above, namely, 475 c.c. One may generalize, I believe, with safety, to this extent, and say that when the heart is relatively large, as in valvular lesions with dilatation and hypertrophy, or in cases of chronic nephritis, any exudate which may develop is likely to leave the front of the heart bare, even when the amount of fluid is quite considerable.

## CONCLUSIONS

1. In pericardial effusion the fluid accumulates first along the lower margin of the heart and about the apex, particularly on the diaphragmatic surface of the heart. With small effusions, this is the only place in which fluid accumulates with regularity.

2. The result of the accumulation of the fluid in this position is to push down the left lobe of the liver. This was demonstrable in practically every case, and in many cases it was a very conspicuous feature. Special stress should be laid on this as an early diagnostic sign.

3. The second place in which fluid accumulates is over the great vessels at the base. With small effusions it is occasionally present in sufficient amount to be detected by percussion. With medium sized effusions this layer is generally thick enough to be demonstrable by percussion, and this retrosternal dullness is an important diagnostic sign.

4. With both small and medium sized exudates we were neither able satisfactorily to demonstrate percussion dullness in the fifth right interspace (Rotch), nor could a rounding of the cardiohepatic (Ebstein) angle be made out in a single case.

5. The behavior of the fluid is practically independent of the position of the patient, with effusions of the size represented by the injections.

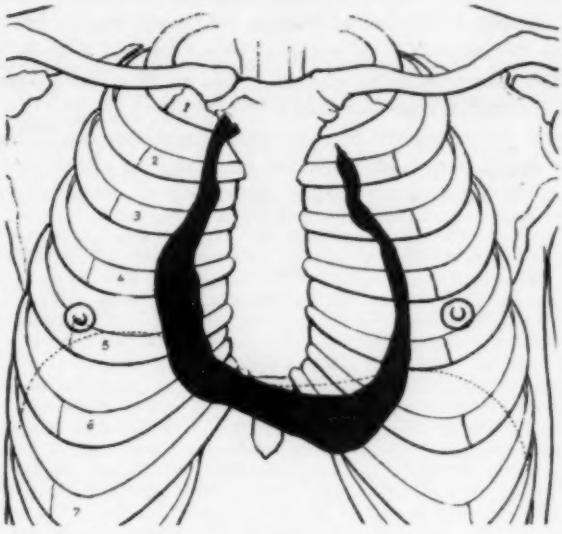


**Fig. 12.—Exp. 28; 655 c.c. injected. The larger portion of the fluid is on the diaphragmatic surface and over the great vessels.** **(See note, page 206.)**

6. In at least fourteen of the thirty-three cases the anterior surface of the heart, in spite of the exudate, remained, in part, uncovered by the fluid, so that a pericardial friction rub could readily exist. This persistence of the pericardial rub is to be anticipated in cases in which the heart is relatively large, so that it fills out the space between the vertebral column and the sternum.

7. From the standpoint of most readily reaching small amounts of fluid, the most appropriate sites for puncture are either just outside the apex or in the chondroxyphoid angle.

# BOOK REVIEWS

SYPHILIS AND PUBLIC HEALTH. By Edward B. Vedder, A.M., M.D., Lieutenant-Colonel, M. C., U. S. Army. Published by permission of the Surgeon-General of the U. S. Army. Cloth, $2.25, pp. 315. Philadelphia and New York: Lea & Febiger, 1918.

Syphilis is one of the most important public health problems and now that the barrier of reticence is breaking down, a serious effort is being made to spread information about the disease and to take counsel openly in the search for methods that will likely diminish its astonishing prevalence. Even physicians who daily in practice see the fatal consequences of this wide-spread and tenacious infection are scarcely prepared to receive without surprise the actual data on the incidence of the disease and the morbidity and mortality it causes. The time has come when public interest will demand of physicians a knowledge of the fundamental facts about syphilitic infection and the physician must be prepared to answer the demand either of individual persons or of community groups eager to help curtail this public evil. It is very convenient to have these fundamental facts so painstakingly and so clearly assembled as they are in Dr. Vedder's small book. He has gone to original sources for his information and each chapter is followed by a valuable list of references. The prevalence of syphilis, sources of infection and methods of transmission, personal prophylaxis, and public health measures are all satisfactorily considered. A very sane and reasonable attitude is maintained throughout the book, noticeable particularly in his discussion of bitterly contested points, as for instance the propriety of advocating and disseminating information on methods of venereal prophylaxis. The book is written clearly and in simple language so that an intelligent layman may easily understand it. It might with profit be recommended to medical students.

NEOPLASTIC DISEASES. By James Ewing, A.M., M.D., Sc.D., Professor of Pathology at Cornell University Medical College, New York City. Cloth. Price, $10.00 Pp. 1027, with 479 illustrations. Philadelphia and London: W. B. Saunders Company, 1919.

Dr. Ewing describes the purpose of his book in the preface. "He has endeavored to analyze the numerous etiologic factors which meet in such diverse fashions in the inception of tumors, to emphasize the general dependence of clinical course upon histologic structure, to trace the histogenesis to the last degree, impressing its essential importance when known, and to enumerate and contrast the more striking clinical features which are often highly characteristic of different tumors. After a brief section dealing with the general principles of oncology the author discusses the different types of tumor and then the varying manifestations of tumors in different regions. Growths are considered regionally rather then histogenetically, a plan that adds greatly to the value of the book from the physician's point of view. Under each organ the different types of tumors that affect it are discussed, the varieties, the etiology, the pathological anatomy, the prognosis and the symptoms. The reviewer has found the book very valuable to himself and recommends it heartily. A great mass of information has been carefully gathered and arranged in easily accessible form. The book is filled with good illustrations, and a carefully selected bibliography serves as a guide to more detailed information upon each topic.

Fifty cents each will be paid for the following issues of the Archives of Internal Medicine: January, March, June, August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.